Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

JULY--1960
Volume 10 - Number 7

Today she is a babysitter—with her own grandchildren. Yet even a generation before she might never have known the joys of marriage and family. Here is a story shared by thousands who lead active lives today because of modern anticonvulsant therapy. Rarely has the progress of medicine touched so many lives with such drama and humanity. Presented here are five distinguished anticonvulsants. They can help you give the most precious of all gifts: a normal life.

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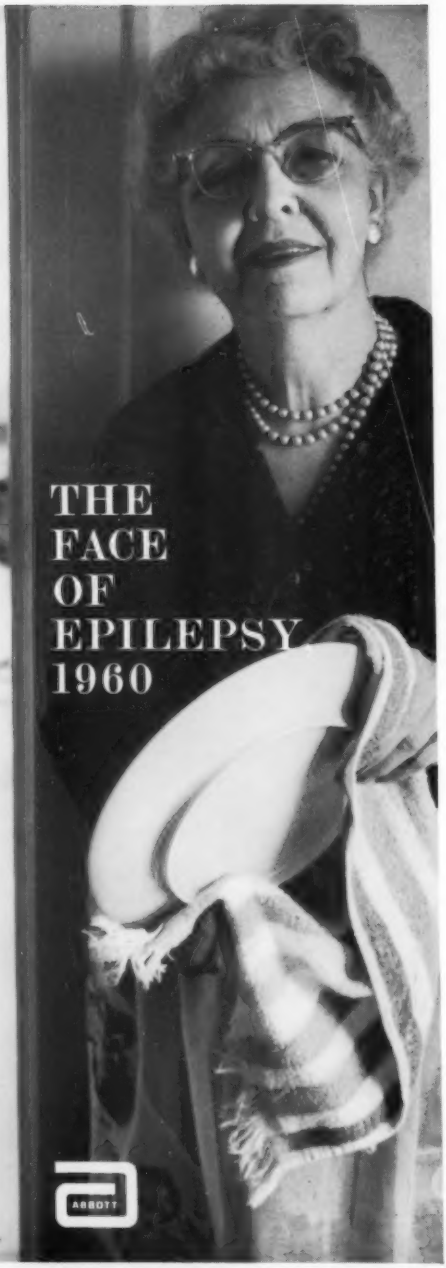

Dynamic Myelography

These two radiographs of the same patient demonstrate the bulging of the annulus fibrosus during hyperextension and flexion, respectively, of the vertebral column. 30 cc of *Pantopaque* contrast medium was used. Note how this technique permits visualization of the posterior surface of the vertebral canal.

"PANTOPAQUE" *is the registered trademark under which all leading x-ray dealers supply the compound ethyl iodophenylundecylate, which is synthesized by the Research Laboratories of Eastman Kodak Company and prepared as the myelographic contrast medium Iophendylate Injection, U.S.P., by Lafayette Pharmacal Inc. The trademark serves to indicate to the radiologist continuity of experience in the manufacture of this medium.*

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Volume 10 **Neurology** Number 7

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Type of Seizure	Number of Patients	Completely Controlled	50-90% Improved	<50%
Grand Mal	214	172 (80%)	15 (7%)	27 (13%)
Psychomotor	29	19 (65%)		10 (35%)
Focal Jacksonian	19	19 (100%)		

Results in 835 epileptic patients who had failed to respond successfully to other anticonvulsants. "Mysoline" was added to current medication which, in some cases, was eventually replaced by "Mysoline" alone.

Type of Seizure	Number of Patients	Completely Controlled	50-90% Improved	<50%
Grand Mal	613	175 (28.5%)	253 (41.2%)	185 (30.3%)
Psychomotor	130	10 (7.7%)	65 (50%)	55 (42.3%)
Focal Jacksonian	92	14 (15.2%)	36 (39.1%)	42 (45.7%)

The dramatic results obtained with "Mysoline" advocate its use as first choice of effective and safe therapy in the control of grand mal and psychomotor attacks. Literature and bibliography on request.

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INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

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1. Schwab, R. S. and England, A. C.: *J. Chron. Dis.* 8:488 (Oct.) 1958.
2. Schwab, R. S.: *Geriatrics 14*:545 (Sept.) 1959.
3. Doshay, L. J. et al.: *J.A.M.A. 160*:348 (Feb. 4) 1956.

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*Kinross-Wright, J.: Newer phenothiazine drugs in treatment of nervous disorders. J.A.M.A. 170:1283, July 11, 1959.

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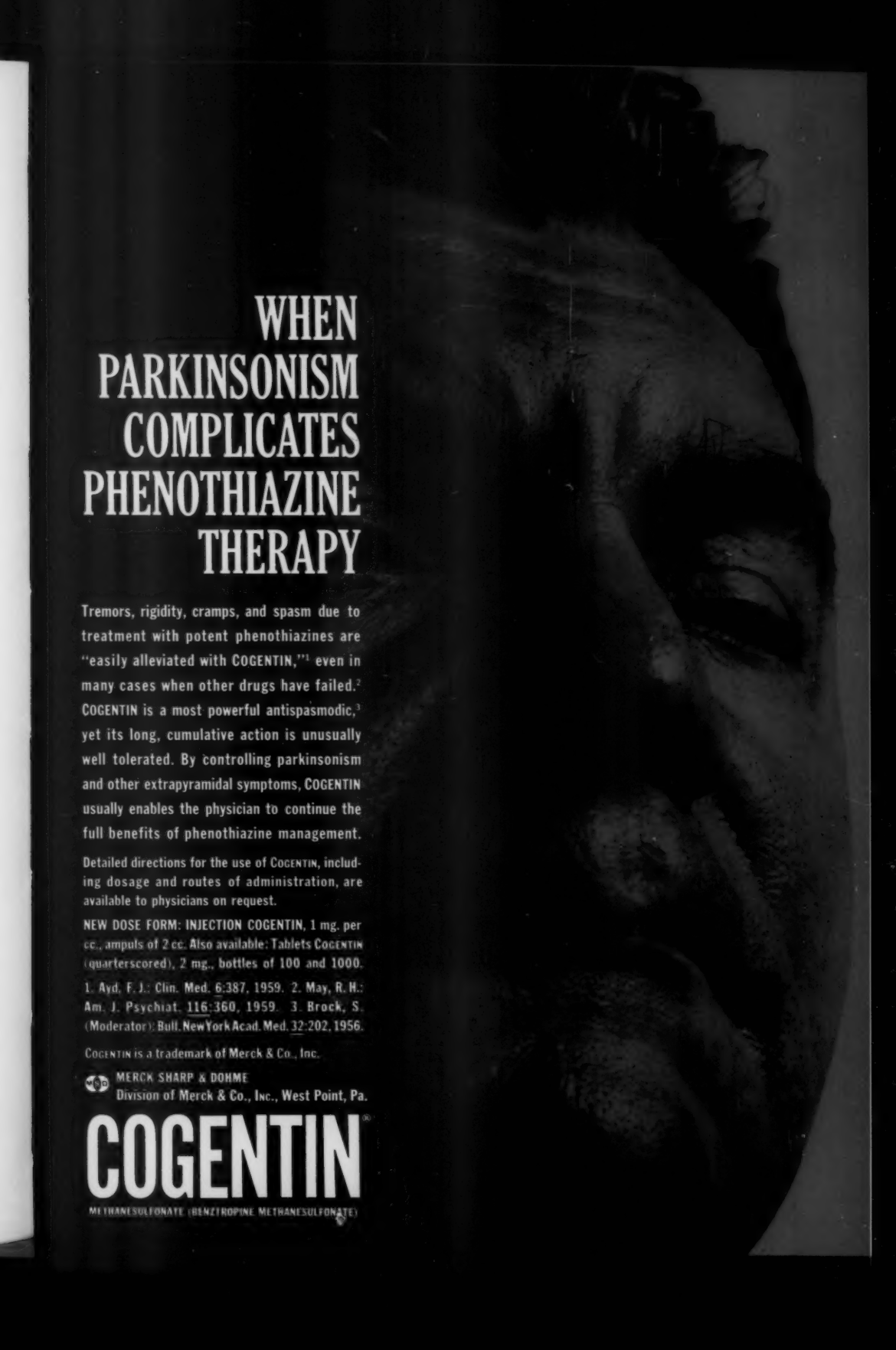
1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.



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1. Ayd, F. J.: Clin. Med. 6:387, 1959. 2. May, R. H.: Am. J. Psychiat. 116:360, 1959. 3. Brock, S. (Moderator): Bull. New York Acad. Med. 32:202, 1956.

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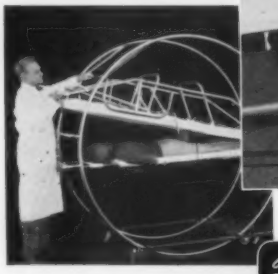

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by Catherine E. Spears, M.D.

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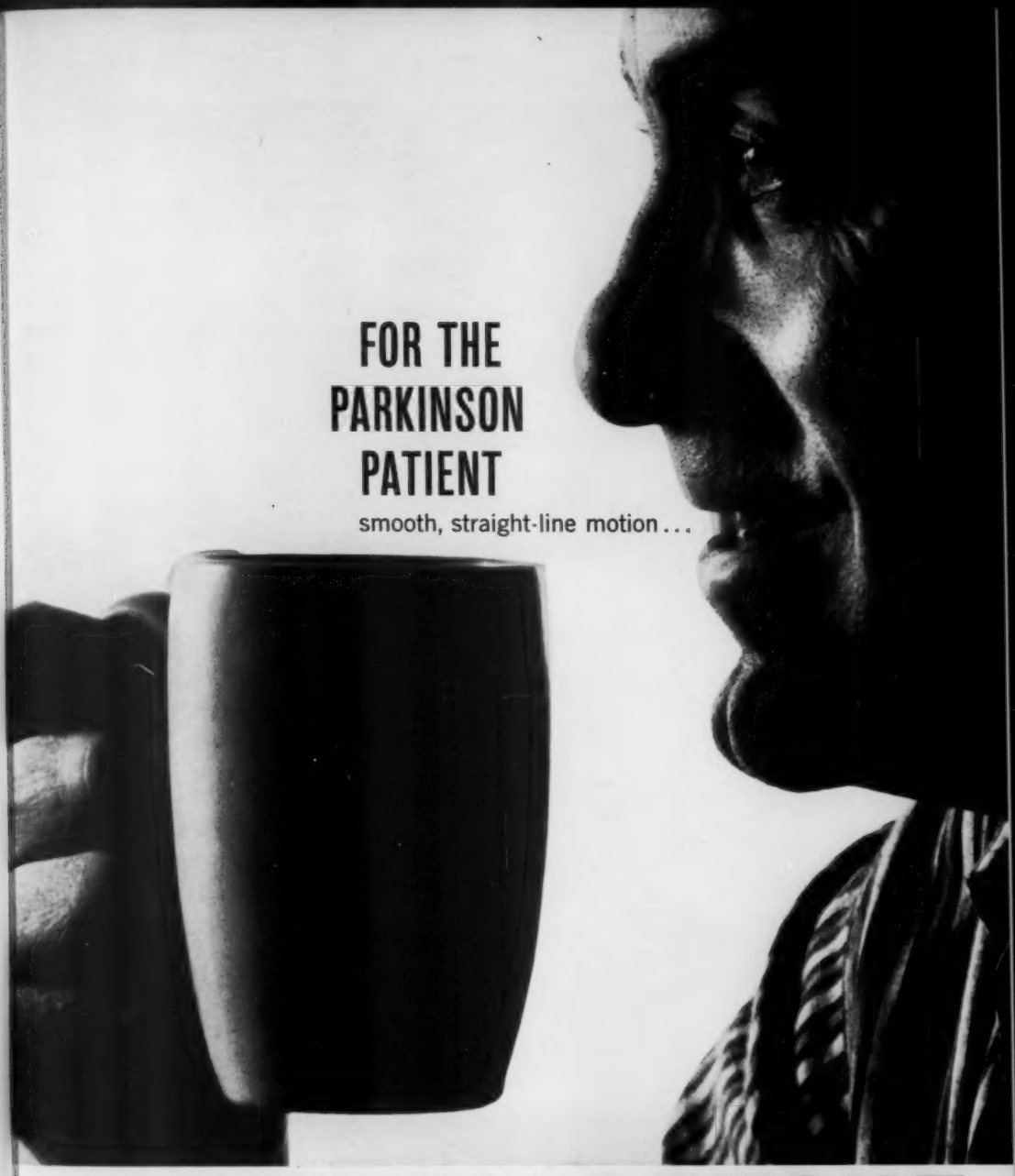

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1. Critchley, M.: British M. J. 2:1214 (Nov. 15) 1958.
2. Doshay, L. J.: Current M. Dig. 22:11 (Nov.) 1956.
3. De Jong, R. N.: J. Michigan M. Soc. 57:722 (May) 1958.

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*K. R. Magee and M. R. Westerberg, **Neurology, 9**:348, 1959.

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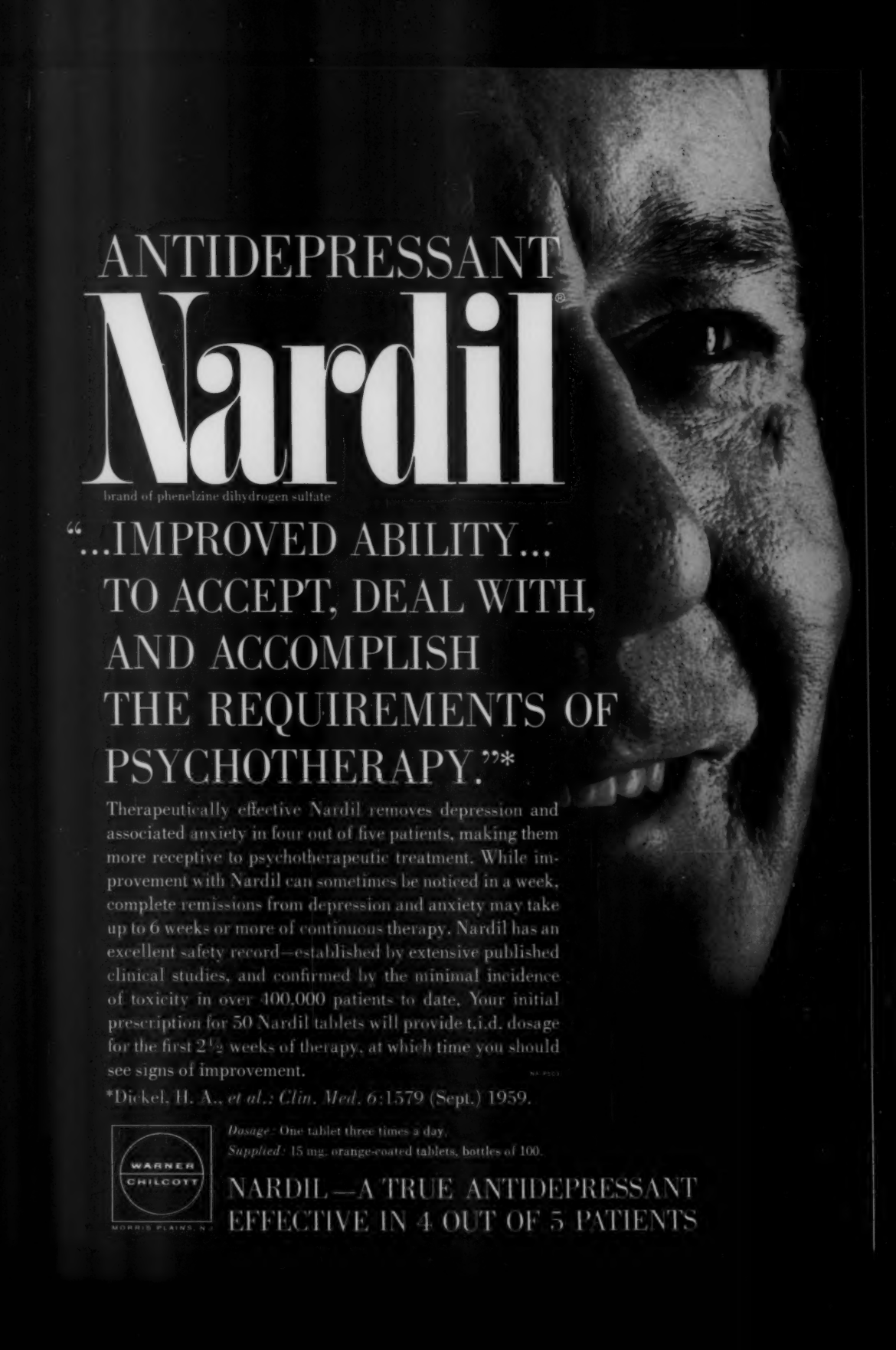

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Simultaneous determinations of retinal and carotid artery pressures

Comparison of per cent reductions after occlusion of the common carotid artery

George T. Tindall, M.D., Herbert T. Dukes, M.D., Horace B. Cupp, Jr., M.D., and Noble J. David, M.D.

DETERMINATION of retinal artery pressures by ophthalmodynamometry has proved useful in the diagnosis of thrombosis of the internal carotid artery since a lower pressure in the eye on the side of the occlusion is usually observed. A significant reduction in the ipsilateral retinal artery pressure also occurs after ligation of the common or internal carotid arteries, and it has been suggested that ophthalmodynamometry be used to evaluate the effectiveness of carotid artery ligation in reducing the distal intravascular pressure.[1–6] Whether the degree of reduction in retinal and distal carotid artery pressures is similar immediately after occlusion of the carotid artery is unknown, as simultaneous retinal and carotid artery pressure measurements have been determined in only a few cases.[2] The present study was undertaken to compare the pressure changes in the retinal artery with those in the carotid artery distal to the site of occlusion. Simultaneous intracarotid and retinal artery pressure recordings were obtained and the per cent reductions in each determined after occlusion of the common carotid artery. The results indicate that, although in most cases the per cent reductions in the 2 measurements are similar, the technic of ophthalmodynamometry alone cannot be relied upon in an individual case to determine the intravascular pressure changes distal to occlusion of the carotid artery.

METHOD

Comparative studies of retinal and carotid artery pressures were made in 13 patients during percutaneous carotid arteriography and in 2 cases during operative exposure of the carotid vessels in the neck. In 2 patients, bilateral studies were done, making a total of 17 observations. Similar studies were carried out in an

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additional 2 patients with complete thrombosis of the internal carotid artery during arteriography in 1 and during operative exposure of the cervical carotid artery in the other. All patients studied showed no evidence of retinal abnormalities, glaucoma, or increased intracranial pressure.

The intracarotid pressure recordings were made using a 17-gauge needle in those patients undergoing arteriography, while a 23-gauge needle was used in those in whom the carotid vessels were exposed. A Sanborn electromanometer with a constant flushing device was used to obtain a continuous intracarotid pressure recording in each patient. Retinal artery pressures were measured with a Bailliart ophthalmodynamometer. The manner in which systolic and diastolic retinal artery pressures were obtained has been described elsewhere.[7] To facilitate funduscopic observation, the pupils were dilated with 10% Neo-Synephrine.

Retinal artery pressures were measured while a continuous intracarotid pressure was being recorded. As each systolic and diastolic retinal artery pressure was obtained, the intracarotid pressure record was marked by means of a foot switch to insure simultaneous determinations. An attempt was made to obtain 3 control readings in each case. The common carotid artery proximal to the needle tip was then occluded by digital compression, and 2 or 3 separate systolic and diastolic retinal artery pressures were taken, care again being taken to mark the intracarotid pressure record as each retinal artery pressure was obtained. Both retinal artery and intracarotid pressures were converted into mean pressure by adding one third of the pulse pressure to the diastolic value. A single average value for both retinal and intracarotid pressures was calculated before and during occlusion of the carotid artery. In 3 instances, only diastolic retinal artery pressures were available, the systolic pressure being in excess of the highest value registered on the instrument (150 gm. of water). In these cases, the per cent reduction in only the diastolic intracarotid and retinal artery pressures were compared.

RESULTS

Patients with a patent carotid system. The per cent reduction for retinal artery and intracarotid pressures after carotid occlusion are shown in Table 1. In 6 of 17 determinations, the difference between the per cent reduction in simultaneously determined retinal artery and intracarotid pressures was less than 5. In 11 out of 17, it was less than 10, and, in 6, the difference ranged from 11 to 22.7. In patient No. 13, the mean retinal artery pressure showed a paradoxic increase during carotid compression, whereas patient No. 10 showed a slight rise in arterial pressure during carotid compression. Patient No. 3, in whom bilateral studies were done, showed a close correlation between the per cent reduction in retinal artery and intracarotid pressures on the left side, whereas the right side showed a wide difference in the per cent reductions. In most cases, the per cent reduction in the arterial pressure was greater than the per cent reduction in the retinal artery pressure.

Patients with thrombosis of the internal carotid artery. Simultaneous determinations of the retinal and carotid artery pressures were made in 2 patients with complete thrombosis of the internal carotid artery (Table 2). In both patients, the retinal artery pressure in the ipsilateral eye before the study was significantly less than in the other eye. Manual occlusion of the common carotid artery on the side of the thrombosis produced a significant further reduction in retinal artery pressure in both cases. A significant difference was found between the per cent reductions in retinal and carotid artery pressures after occlusion in patient No. 1. The per cent fall in the intracarotid pressure was 60 and in the retinal, 35, a difference of 25. The second patient, however, showed practically equal reductions in the retinal and carotid pressures after occlusion of the carotid artery, despite the fact that the internal carotid artery at its origin was completely occluded by a thrombus.

DISCUSSION

It has been shown that, after occlusion of the common carotid artery, the per cent fall in intravascular pressure is the same in all portions of the internal carotid and its accessible branches.[8,9] Since the ophthalmic artery is a branch of the internal carotid artery, it is reasonable to assume that the per cent reduction in intravascular pressure in the ophthalmic

TABLE 1

PER CENT REDUCTION IN RETINAL AND DISTAL CAROTID ARTERY PRESSURES AFTER OCCLUSION OF THE COMMON CAROTID ARTERY

Case	Per cent reduction		Difference
	Retinal artery pressure	Carotid artery pressure	
1	34.7	33.3	1.4
2	48.2	46.6	1.6
3 OS	33.0	30.0	3.0
3 OD	24.3	40.5	16.2
4	59.4	62.6	3.2
5	32.4	29.0	3.4
6 OD	19.0	23.0	4.0
6 OS*	19.3	25	5.7
7	20.7	27.1	6.4
8	17.4	24.6	7.2
9	29	36.2	7.2
10	3.3	+ 5.5	8.8
11	33	22	11
12*	19	30.8	11.8
13	+ 10.6	6.2	16.8
14*	8.1	25	16.9
15	14.3	37	22.7

*Diastolic retinal and carotid pressures only

and internal carotid arteries will be similar after occlusion of the common carotid artery. According to Duke-Elder,[10] the determination of retinal artery pressure by ophthalmodynamometry is actually a measure of lateral pressure in the ophthalmic artery.

Rand[2] showed a close correlation in one patient in the per cent reduction of simultaneously determined retinal and intracarotid pressures after occlusion of the carotid artery. A close correlation between the per cent reduction in retinal and carotid artery pressures was noted in the majority of the patients in the present series. However, in a few cases, the difference between the per cent reductions in simultaneously determined retinal and carotid pressures was such that the technic of ophthalmodynamometry could not be reliably used as a quantitative measure of the changes in intravascular pressure above the site of carotid occlusion. The reasons for the relatively wide difference in some cases between the per cent reduction in the 2 measurements are not entirely clear. Undoubtedly the commonly used technic of obtaining systolic and diastolic end points in ophthalmodynamometry offers a considerable potential source of error, especially if the pulse is slow or irregular. This factor did not seem to be important since all of our patients were cooperative, all had regular cardiac rhythms, and the results were reproducible. The differences may be related to anatomic factors. In those patients in whom the per cent reduction in retinal artery pressure is significantly less than the simultaneously determined per cent reduction in carotid artery pressure, it is possible that a significant per cent of the

TABLE 2

PER CENT REDUCTION IN RETINAL AND DISTAL CAROTID ARTERY PRESSURES AFTER OCCLUSION OF THE COMMON CAROTID ARTERY IN PATIENTS WITH COMPLETE THROMBOSIS OF THE INTERNAL CAROTID ARTERY

Case	Per cent reduction		Difference
	Retinal artery pressure	Carotid artery pressure	
1	35	60	25
2	39	40	1

blood supply to the retinal artery is from some source other than the ipsilateral internal carotid artery.

The present study sheds further light on the role of the external carotid artery in maintaining the retinal artery pressure in instances of thrombosis of the internal carotid artery. In both cases of complete thrombosis of the internal carotid artery in the present series, occlusion of the common carotid artery produced a further significant drop in the ipsilateral retinal artery pressure. In one instance, the per cent fall in the retinal artery pressure was equal to the per cent fall in the common carotid artery, a finding which suggests that the major portion of the blood supply to the retinal artery in this case was via the ipsilateral external carotid artery.

SUMMARY

Comparative per cent reductions between the retinal artery and intracarotid pressures after occlusion of the common carotid artery were determined in 17 instances in 15 patients. Similar studies were carried out in 2 additional patients with complete thrombosis of the internal carotid artery. A good correlation between the per cent reductions in simultaneously determined retinal artery and intracarotid pressures was obtained in most cases. However, in a few, the difference between the per cent reductions in simultaneously determined retinal and carotid pressures was such that the technic of ophthalmodynamometry could not be reliably used as a quantitative measure of the changes in intravascular pressure above the site of carotid occlusion.

A significant further reduction in ipsilateral retinal artery pressure followed occlusion of the common carotid artery in both patients with complete thrombosis of the internal carotid artery.

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CASE REPORT

Hereditary sensory radicular neuropathy

A. J. Mandell, M.D., and C. K. Smith, M.D.

THE FAMILIAL and sporadic occurrence of trophic ulceration in the lower extremity associated with progressive peripheral sensory loss of an unusual type, without clinical evidence of disease of the motor system, has been repeatedly described and variously named since the report of Verhoogen and Vandervelde[1] in 1894. The precise pathologic alterations caused by the disease were unknown until Denny-Brown's[2] analysis of postmortem material from one of Hick's[3] cases, which was later confirmed by others.[4,5] The condition was shown to be a degenerative disease of the nervous system with the primary pathologic alterations in the dorsal root ganglia of the spinal cord segments supplying the limbs. Most of the previous reports have come from Europe, but a few groups of cases have been reported from the northern and midwestern United States.[6–9] The following is an account of a familial case from Florida and demonstrates the typical history and physical findings of this unusual disease.

CASE REPORT

R. B., a 30-year-old lumberyard clerk, was first seen on May 4, 1959, because of recurrent, painless ulcerations of the feet of three years' duration. His initial symptom was a vague numb feeling at the tips of the toes of the left foot in 1950, first noticed when his toes seemed insensible to the temperature of bath water. Later, this sensation was noted in the right foot. About the same time, his feet began to perspire a great deal. The sensory loss was progressive, and, by 1955, lacerations and punctures on his feet were painless. One day in 1956, he walked around for several hours before noticing a thumbtack sticking in the fourth toe of his right foot. Shortly after this, he began to note thermoanalgesia in his fingers that was associated with increased perspiration in his hands. In 1957, a callus formed in the skin beneath the first metatarsophalangeal joint of his right foot. It later became "dark" and spontaneously and painlessly drained. In spite of rest and medical therapy, the resulting ulcer drained for fourteen months. In September 1958, the same area on the left foot ulcerated, and, in the ensuing months, small spicules of bone extruded.

In 1956, the patient began to notice severe, burning pains in the third, fourth, and fifth fingers of each hand, lasting one to two minutes. Rubbing and squeezing these fingers hastened the termination of the pain. The pain occurred several times a week and had continued up to the time of admission. He had no pains in his legs or feet and did not complain of motor weakness or incoordination.

Numerous medical examinations, including detailed investigation for diabetes, failed to disclose any abnormalities. Spinal fluid examination in a Florida hospital in 1958 showed nothing of note. Many courses of oral and parenteral vitamin therapy had proved of no value.

The patient's father (Case 6) had been afflicted with a similar malady. Beginning at the age of 23 years, he suffered from recurrent ulcers associated with extrusion of bone and loss of sensation in the lower extremities, which was variously diagnosed as "diabetes without kidney sugar," "multiple sclerosis," and "vitamin deficiency." He also suffered from shooting pains in his hands. He succumbed to a disease consisting of high fever and "boils all over" at the age of 43 years. The patient's

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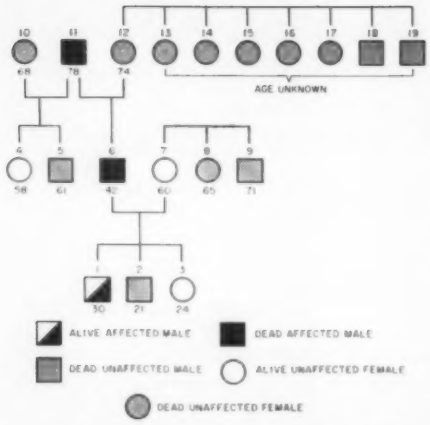

Fig. 1. Geneologic table representing affected and nonaffected members of the family. The numbers underneath each figure indicate the age at death or the present time. The numbers above represent the case designation.

paternal grandfather (Case 11) also had recurrent ulcerations of the feet beginning in the fourth decade of life, which finally necessitated amputation of a leg in the sixth decade (Fig. 1). The patient's family has lived in Florida for at least 4 generations.

At the admission examination, arterial pulses including the dorsalis pedis and posterior tibial were full. Hands, feet, and legs were erythematous and moist. The subcutaneous tissue of the toes, especially the large ones, was swollen. Ulcerations with trophic changes in the skin were present bilaterally (Fig. 2).

On examination of the motor system, the tone and strength were normal and there was no evidence of fasciculations or muscular atrophy. Fine and alternating movements were normal in the upper and lower extremities. The Babinski, Chaddock, Romberg, and Oppenheim signs were absent. Abdominal superficial reflexes were present in all quadrants. Deep tendon reflexes were brisk and symmetric except for the Achilles reflexes, which were

Fig. 2. Trophic ulcerations and scaling seen on both the dorsal *(left)* and ventral *(right)* aspects of the feet

barely elicitable. The cranial nerves and fundus appeared normal. Hearing was excellent, and results of the Rhine and Webber tests were normal.

On sensory examination, a peripheral loss of pain, temperature, and touch was noted, with considerably greater loss of pain and temperature than touch. Little loss of vibratory, passive motion, or position sense in the limbs was found. The sensory loss was bilateral in the seventh cervical through the second thoracic and the fourth lumbar through the first sacral dermatomes (Fig. 3).

Hemoglobin, hematocrit, white blood cell count, differential count, blood urea nitrogen, and fasting blood sugar values were within normal limits. The Kolmer and Kahn reactions were negative. Sedimenation rate was 69 mm. (Westergren), which was thought to reflect the ulcerative process on the feet. The spinal fluid contained 9 white cells per cubic millimeter, 74 mg. per cent of sugar, and a protein of 26 mg. per cent. The Pandy reaction showed no increase. The electrocardiogram and roentgenograms of the chest and skull showed no abnormalities. Roentgenograms of the lumbosacral spine revealed no vertebral deformity or interspace narrowing suggesting a dysraphic state. Roentgenograms of the left foot revealed fragmentation and dissolution of the bony structure of the proximal phalanx, leaving only bony debris. Fragments near the proximal articular surface showed increased density as did the tuft of the distal phalanx. The same kind of changes were seen in the right foot (Fig. 4).

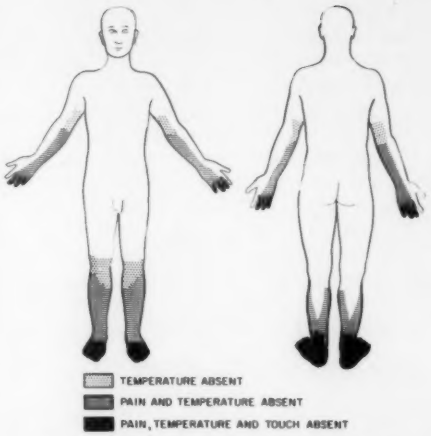

Fig. 3. Dermatome representation of the sensory loss. Vibratory, position, and passive motion sensibilities were intact.

DISCUSSION

A few rather complete historical reviews of this subject have appeared during the last several years.[2,4,6,8] Using recently acquired pathologic material, Denny-Brown and others[2,4,5] cleary differentiated this disease from lumbosacral syringomyelia, status dysraphicus, Morvan's disease, myelodysplasia, familial peripheral neuropathy, amyloidosis, tabes dorsalis, congenital indifference to pain, neurofibromatosis, and leprosy, conditions with which it had been previously confused. The clinical picture that most closely resembles this one is the rare symmetric sensory neuritis of longstanding diabetes.[10] The numerous failures to demonstrate diabetes as well as the early age of onset makes this diagnosis untenable in our case. The disease differs from the more common diabetic radiculoneuropathies in that vibratory and passive motion sensibilities are considerably less affected than those of pain and temperature.

The age of onset of symptoms in the reported cases ranges from 4 to 51 years, usually beginning in young adulthood.[8] The disease has been reported in males and females alike in both familial and sporadic cases. Results of spinal fluid examinations have been normal.

The patient in the case reported by Denny-

Fig. 4. Roentgenograms of both feet showing fragmentation and dissolution of the bones of the phalanges

Brown[2] showed degeneration and disappearance of nerve cells of the dorsal root ganglia, which was most noticeable in the lower lumbar and upper sacral cord but was also seen in the eighth cervical and first thoracic segments. The ganglia showed proliferation of the capsule cells and deposition of a hyaline material that stained variably with Congo red. The ventral roots were intact. Some degeneration was seen in the dorsal columns of the spinal cord up to the level of the medulla. The hyaline material failed to stain with Congo red in van Bogaert's case[4] and was reported absent in Blackwood's material.[5] It is thought that this material is a result rather than the cause of the dorsal root ganglion cell degenerative process.

Thus far, two reasons have been advanced for the type of sensory loss initially seen in this disease. One is the preponderant selective loss of the smaller ganglion cells subserving pain and temperature sensation.[11] The other is production of a condition analagous to surgical sectioning of a single dorsal root, which results in sensory loss more extensive for pain and temperature than for touch.[2]

The trophic changes of ulceration and bony dissolution were attributed by Denny-Brown to repeated, painless trauma and resulting infection. In our patient, the cutaneous vascular and sudomotor abnormalities with the same distribution as the loss of temperature sensation suggests more complex pathophysiology than this. One might speculate that the loss of the modulating afferent limb of autonomic reflexes[12] or the abnormal reactions of the dorsal root vasodilator fibers[13] produce vascular stasis and pronounced local diaphoresis, which in turn contribute to the trophic changes. Mulvey and Riely's[6] patients had reduced or absent histamine flares over the area of thermoanalgesia. These flares have been recently shown to be dependent upon dorsal root integrity.[14]

The familial cases reported previously have shown this to be a Mendelian dominant trait,[2,4,5] and the geneology in our case is consistent with this. Hereditary deafness has been reported in a few of these families,[3,5] resulting from degeneration of cells in Scarpa's ganglia. The family of the patient herein described as well as most of the others who have been reported in the literature did not show this feature.

Several authors[2,7,8,15] reported sporadic cases resembling the familial ones in detail, and we recently had an opportunity to examine a 52-year-old man from New Jersey with longstanding, recurrent, symmetric ulcerations of the lower extremity associated with changes in bone and a typical sensory deficit. He did not give a family history of a similar disease and did not have diabetes.

SUMMARY

A typical case of hereditary sensory radicular neuropathy with recurrent ulcerations and arthropathy in the lower extremities and a radicular sensory deficit of the upper and lower limbs without evidence of motor dysfunction has been presented. The geneologic information presented is consistent with previous descriptions of this disease as a Mendelian dominant trait, but sporadic cases are also recognized.

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Permeability of cerebral vessels to albumin in hyperbilirubinemia

Observations in newborn animals

B. Rozdilsky, M.D., M.Sc., Ph.D., and J. Olszewski, M.D., Ph.D.

THAT BILIRUBIN exists in the circulating blood in the form of bilirubin-albumin complex is generally accepted.[1–3] A number of clinical observations indicate that, in neonatal jaundice, both the cerebrospinal fluid proteins and bilirubin are raised.[4,5] The same observations and the results of some experimental work[6] suggest that bilirubin enters the cerebrospinal fluid while still attached to molecules of albumin. However, it is not known in what form bilirubin crosses the blood-brain barrier and reaches the nerve cells, thus producing kernicterus. One could postulate that at least a certain portion of serum bilirubin pentrates the nervous tissue in the form of albumin complex.

Most recent developments in the study of neonatal hyperbilirubinemia point to the importance of dissociated, protein-free bilirubin in the production of brain damage.[7,8] According to this new concept, the unbound bilirubin is the main form or possibly the only form[9] that penetrates through the semipermeable membranes of the cells. Nevertheless, a protein indicator appears to be useful for the study of the permeability of cerebral vessels to bilirubin, since information obtained from such investigations would apply equally to both forms of bilirubin, with or without a protein carrier. If a vessel becomes permeable to large molecules of albumin, it would obviously be permeable to dissociated bilirubin and most probably to the bilirubin-albumin complex. As a consequence, any new data pertaining to the permeability of the cerebral vessels to molecules of serum albumin, in particular in the neonatal period and during hyperbilirubinemia, would be of value for better understanding of the pathogenesis of human kernicterus. This report deals with results obtained during a study of the permeability of cerebral vessels to iodinated I^{131} bovine albumin in newborn animals with experimental hyperbilirubinemia. It is a part of a broad research project on the blood-brain barrier investigated with radioactive albumin and an autoradiographic technic.[10–13]

MATERIAL AND METHODS

In this work, fifteen newborn rabbits of average weight 40 to 60 gm., 9 newborn puppies of 250 to 270 gm., and 9 newborn kittens of 100 to 120 gm. were used. Out of this number, 6 rabbits, 3 puppies, and 3 kittens served as controls. The remaining 9 rabbits, 6 puppies, and 6 kittens received injections of bilirubin-albumin complex prepared according to the following method of Ruthven and Lathe.[14]

"Grind 50 mg. of bilirubin, with the aid of a glass rod, with 0.75 N NaOH in a small thick walled tube. Add the caustic in small aliquots until this bilirubin is in solution. Centrifuge, take off the supernatant, and add a trace more soda to any residue, treat this mixture as before and add the spun solution to the previous supernatant. In all, about 0.3 ml. 0.75 N NaOH should be required. Add the caustic-bilirubin solution, with stirring, to 0.8 ml. of 30% w/v bovine albumin, the *p*H of which has been previously adjusted with a little caustic to about eight. This bilirubin-albumin solution is immediately neutralized to *p*H 7.6. This step is very critical, and is done by

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adding slowly 1.0 M KH_2PO_4 from a microsyringe, through a hypodermic needle, to the rapidly stirred (mechanical if possible) bilirubin-albumin solution. About 0.1 ml. of the KH_2PO_4 is required. The bilirubin-albumin solution at *p*H 7.6 is finally clarified by centrifuging, and the supernatant is used for injection."

The treatment was similar to that in a study on the toxicity of bilirubin, which will be reported elsewhere.[15] The animals were given an intravenous injection of the solution in an amount corresponding to 1 mg. of crystalline Eastman Kodak bilirubin per 10 gm. of body weight. In order to maintain the concentration of bilirubin in the serum between 50 and 20 mg., repeated injections were given. The 9 rabbits were reinjected with one half of the initial dose of bilirubin eight hours after the first injection. Two hours after the second injection, 0.2 cc. of 2% iodinated bovine albumin corresponding to 40 μc. was injected intravenously. In the 6 puppies and 6 kittens, 2 additional injections, each with one half of the initial dose, were given, the first five hours and the second thirteen hours after the initial injection. The second reinjection was followed in three hours by radioactive bovine albumin in the amount of 75 μc. for the puppies and 50 μc. for the kittens.

Out of the control group, 5 rabbits, 2 puppies, and 2 kittens received intravenous injections of a solution that contained all the ingredients in the same proportion as in the solution of bilirubin-albumin complex, except for the omission of bilirubin. The volume injected, the time intervals, and the final dose of radioactive albumin were the same as in the previous groups.

Two hours after the injection of radioactive albumin, the animals were killed by a hemodilution technic. This was a modification of the method developed earlier for adult animals[10] and found to be essential for the complete removal of the residue of radioactive blood from the vessels of the brain. The animals were fastened supine to a board. Under light ether anesthesia, one of the external jugular veins was punctured with 27-gauge long needle connected to the rubber tubing of a transfusion set of 6% dextran. (The assistance of Abbott Laboratories, Ltd., in donating dextran for this study is acknowledged). The other external jugular vein was cut, and the fluid was injected at a rate of approximately 1 drop per second. Care was taken that the loss of blood should be compensated by the amount of plasma substitute infused. When the animals died from hemodilution, the chest was opened and the left ventricle of the heart was punctured with 22-gauge needle connected to a perfusion set of physiologic saline. The fluid was introduced at the pressure of 10-cm. column of water for the rabbits, 20 cm. for kittens, and 30 cm. for puppies. Only a small volume of saline was used, not exceeding 10 to 30 cc., depending upon the size of the animal. The perfusion with saline was followed by perfusion with 10% formalin, and the brains were removed and fixed in 10% formalin for twelve hours. Then they were cut in coronal plane and examined for the presence of jaundice or any gross pathologic change. Multiple color photographs were taken. In the next step, frozen sections were cut 25 μ. thick, mounted, and dried and contact autoradiographs with "No Screen" x-ray film were made. The exposure was seventy-two hours. The histologic slides were stained subsequently with cresyl violet and correlated with the autoradiographs.

An additional control animal of each species that had not been treated at all was given the injection of radioactive albumin only and was sacrificed two hours later. Perfusion was omitted. The brains were removed and processed in the way described above.

RESULTS

Autoradiographs of the nonperfused rabbit's brain disclosed the vascular pattern of the brain with a generalized slight radioactivity in the background. No particular regions of the gray matter stood out as especially radioactive (Fig. 1).

Gross examination of the brains of the rabbits treated with bilirubin showed absence of icteric discoloration of nervous tissue except for the choroid plexus, which was intensely jaundiced. Autoradiographs were of essentially the same appearance in the animals treated with bilirubin and in the perfused controls (Fig. 2). In both instances, the same sharp, black contour corresponding to the meninges, ependyma, and choroid plexus was found.

Also, in some cases, a fairly intense radioactivity was noted in the brain tissue proper, adjacent to the ventral corners of the lateral ventricles. This radioactivity extended into the nervous tissue for some distance with gradually decreasing intensity. In addition, in almost all brains, the hypothalamus was radioactive.

The control puppy and kitten, which were sacrificed two hours after injection of radioactive bovine albumin and were not perfused, showed a much denser vascularization of the gray matter as compared with the white matter. The dense vascular network was sharply limited to individual masses of the gray matter of the basal ganglia, thalamus, brain stem, and cortex (Fig. 3).

The brains of the perfused control puppies and kittens produced the same autoradiographic effect, in which there was a definite outline of the choroid plexus and a much fainter border of the meninges and ventricular lining (Fig. 4). In certain cases, there was some concentration of radioactivity in the attachments of the choroid plexus and in the hypothalamus.

The autoradiographs of the 6 puppies treated with bilirubin showed no uniform pattern. In 4 brains that did not show gross jaundice, there was no difference as compared with the perfused controls. In the remaining 2 brains, which were pale yellow, the cerebral cortex, basal ganglia (Fig. 5), thalamus, floor of the fourth ventricle, and cerebellum showed an increased concentration of radioactivity, most intense in the layers immediately subjacent to the meninges and ependymal lining and gradually decreasing into the deeper layers of tissue. In 1 case, autoradiographs of the spinal cord were made and showed an intense darkening over the gray matter.

Out of the 6 kittens treated with bilirubin, 4 produced a similar autoradiographic result, which was considerably different from that of other species (Figs. 6 through 9). The whole surface of the brain had a slight background radioactivity that was distinctly accentuated in the thalami, inferior colliculi, gray matter around the fourth ventricle, lateral cuneate nuclei, and, to a lesser degree, the basal ganglia, hippocampi, certain areas of the cortex, and, in one case, segments of the underlying white matter. Correlation of the autoradiographs with photographs of the brains showed the distribution of nuclear jaundice closely coinciding with that of the radioactivity. The autoradiographs of the remaining 2 brains that were not grossly jaundiced differed in no respects from those of the perfused controls.

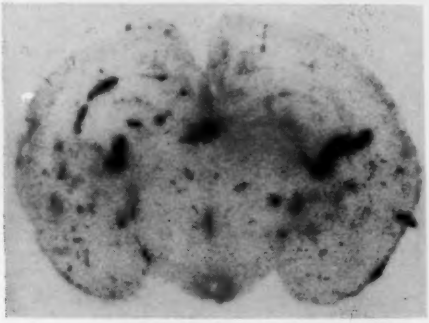


Fig. 1. Autoradiograph of newborn rabbit's brain. No perfusion. Note a slight background radioactivity with numerous dark spots representing the blood vessels; 2 large dark patches overlying the hippocampi and a single dark spot in the midline correspond to the choroid plexus.

DISCUSSION

The problem of the blood-brain barrier in newborn infants and animals is a controversial

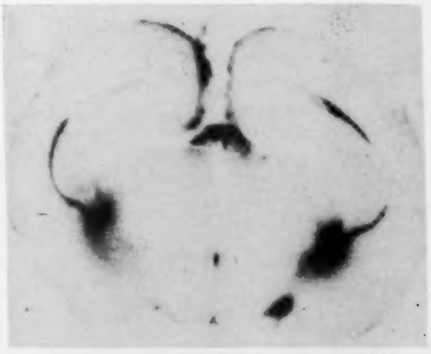


Fig. 2. Autoradiograph of newborn rabbit's brain. This animal was treated with bilirubin and perfused. Note darkening over the meninges, ependyma, and choroid plexus. The meninges remained attached to the cortex over small areas only; 2 patches of diffuse radioactivity lateral to the thalamus correspond to the tissue around the ventral corners of the lateral ventricles.

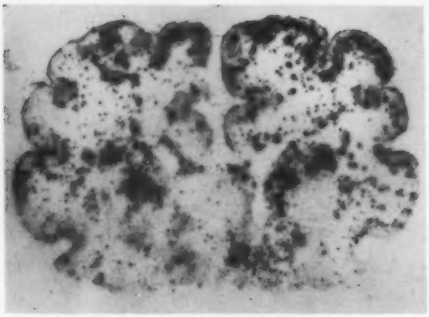


Fig. 3. Autoradiograph of newborn puppy's brain. No perfusion. Note numerous dark spots corresponding to the blood vessels.

Fig. 4. Autoradiograph of newborn puppy's brain. Perfused, untreated animal. Note a minimal darkening over the whole surface of the section with accentuation over the ependyma.

Fig. 5. Autoradiograph of newborn puppy's brain. Treated with bilirubin and perfused. Vascular permeability is increased in the cerebral cortex and portions of the basal ganglia.

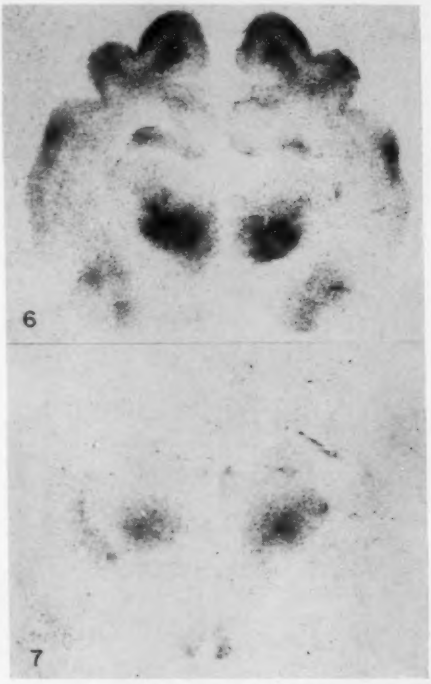
one. Because of the incidence of kernicterus in the neonatal period, it appeared logical to postulate that this protective mechanism of the brain is absent or imperfectly developed at birth. This view was partly based on the findings of Behnsen[16] with trypan blue and of Stern and Peyrot[17] with sodium ferrocyanide, who noted a greater penetration of these indicators into the brains of newborn animals than into those of adult animals. Broman[18] and Gröntoft[19] failed to confirm these observations. Bakay[20] demonstrated that more radioactive phosphorus accumulated in the brains of newborn animals than in those of adults. However, as pointed out by the author, this effect was apparently related to the increassed metabolism of the developing brain. Very recently, Millen and Hess[21] repeated some of the previous work using trypan blue and extended the experimentation to also include a number of hydrogen indicator dyes. They drew the conclusion that, in newborn animals, the barrier between the circulating blood and the nervous tissue is impermeable. However, they admitted that the hematoencephalic barrier in the fetus and newborn animal may be less complete and that the presence or absence of permeability depends to some extent on the test substances used. Our present work lends additional support to the contention that the blood-brain barrier at birth is fairly well developed, at least as far as the permeability of cerebral vessels to molecules of albumin is concerned. However, apart from the usual uptake of radioactive albumin by the hypothalamus, which is also observed in autoradiographs of adult animals, in certain newborn animals there was some darkening over the nervous tissue just under the meninges, into the ependyma and subependymal tissue. This suggests that some penetration may occur from the cerebrospinal fluid after a small amount of proteins entered the fluid from the blood. The presence of radioactivity around the points of attachment of the choroid plexus is difficult to explain. Perhaps it is due to spread of radioactive material by diffusion from the connective tissue of the strongly radioactive plexus to the adjacent nervous tissue. The concentration of radioactivity in the brain tissue around the ventral corner of the lateral ventricles is probably related to some local peculiarities of either

ependymal permeability or tissue architecture. It has also has been observed in other conditions.[12]

The effect of hyperbilirubinemia on the permeability of cerebral blood vessels to protein molecules was not the same in all three species investigated. No change of permeability was produced in any of the rabbits by twelve-hour hyperbilirubinemia. The results obtained in the puppies and kittens are not strictly comparable with those in the rabbits, because the former were exposed to hyperbilirubinemia six hours longer. However, there appears to be a definite difference. A proportion of puppies and kittens showed an increase of permeability that was rather diffuse in the puppies and fairly selective in the kittens. Comparison of the autoradiographs with the patterns of yellow discoloration observed in the same brains indicated that the increased permeability was localized to the regions in which bilirubin stained the brain tissue. We have also observed this selective staining and difference in susceptibility of the various species to nuclear jaundice on larger amounts of material.[15]

We accepted a working hypothesis that, in kernicterus, a certain amount of bilirubin penetrates the hematoencephalic barrier as a complex with molecules of serum-albumin. This hypothesis is supported not only by the results of this study but also by our unpublished observations that, in general, bilirubin passes the blood-brain barrier in all conditions in which the barrier becomes permeable to radioactive albumin. For example, cats were injected intravenously with bilirubin-albumin complex, and air was introduced into one carotid artery. On the corresponding side, the brain showed a faint yellow discoloration. On the contrary, under the same conditions, no jaundice of the brain was produced in rabbits. As reported by Lee and Olszewski,[13] air embolism renders the cerebral blood vessels permeable to radioactive albumin in cats but not in rabbits.

Another example was provided by experiments with intracarotid injection of alcohol. Only a minimal amount of iodinated radioactive albumin entered rabbit brain after intracarotid injection of 15% alchohol, and, similarly, the brain remained unstained if the rabbits were injected intravenously with the bilirubin-albumin complex followed by intracarotid alcohol of the same concentration. However, an intense unilateral cerebral jaundice was noted if 20 to 30% alcohol was used, and such a concentration also produced an increase of permeability to radioactive albumin. Observations suggesting that bilirubin may produce increase of permeability of cerebral vessels detectable by molecules of albumin do not contradict the attractive hypothesis[7,8] that stresses the significance of the dissociated, diffusible form of bilirubin in causing brain damage. In fact, a disturbance of the function of the blood-brain barrier of such magnitude that it allowed the penetration of protein molecules would obviously increase crossing of the barrier by the small particles of dissociated bilirubin. No quantitative estimation was made on the



Figs. 6 and 7. Autoradiographs of newborn kittens' brains. Treated with bilirubin and perfused. Note radioactivity in the thalami and, in Figure 6, in some areas of the cortex and white matter.

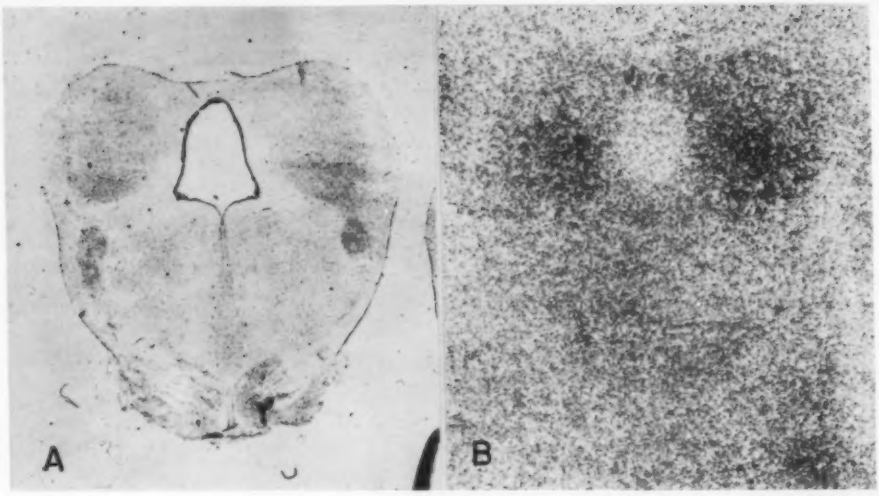


Figure 8

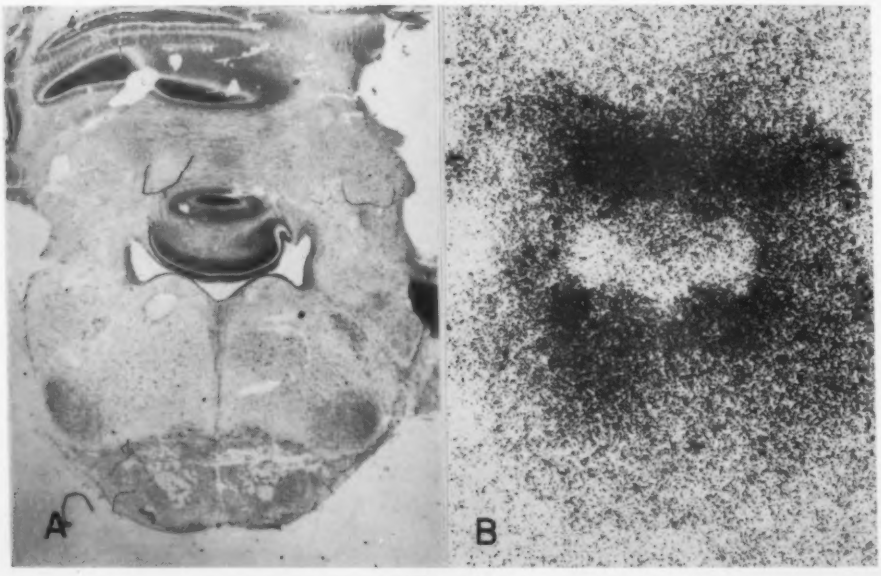


Figure 9

Figs. 8 and 9. Photomicrograms of histologic sections and corresponding autoradiographs. Kittens treated with bilirubin and perfused. In Figure 8, there is darkening of emulsion over the inferior colliculi and, in Figure 9, over the area subjacent to the floor of the fourth ventricle and the deep nuclei of the cerebellum.

amount of albumin indicator that had passed across the blood vessels into the brain tissue. This amount may indeed be very small, and, consequently, we are unable to say to what extent the protein-bound bilirubin could contribute to the production of brain damage.

The possibility that the observed increase of vascular permeability in hyperbilirubinemia might be the result of a nonspecific mechanism like shock or anoxia should be considered. However, the work of Broman[18] speaks against such an alternative. The observations of this author and our own previously reported results[10–13] indicate that the blood-brain barrier is very stable and is not easily damaged by such factors as histamine shock, deep anesthesia, congestion, and hemodilution. In addition, brains of puppies that had died in insulin shock (our unpublished data) also failed to produce autoradiographic patterns comparable to those of hyperbilirubinemia.

In order to produce increased vascular permeability, a high concentration of bilirubin in the blood must be present for a considerable time. If this condition is met, kernicterus may develop, not only in the newborn but also beyond the neonatal period; 2 reports in the literature describe such cases. The first, by Rosenthal, Zimmerman, and Hardy,[22] presents a child from a family with a defect of glucoronide conjugation, who had bilirubin encephalopathy at the age of 3 years. In the second, by Sherlock,[23] a deep jaundice developed in an adult with malignant biliary obstruction. It was associated with well defined basal ganglia signs, and autopsy revealed yellow staining of these structures. The blood had shown a surprisingly high level of indirect reacting bilirubin, which was, in the opinion of the author, the apparent cause of the nuclear jaundice. It should be pointed out that, in both cases, the condition arose at a stage at which the blood-brain barrier was apparently well developed. Thus, there is no need to invoke the concept of absence of the blood-brain barrier in the neonatal period to explain the pathogenesis of kernicterus.

The main conclusion we would like to draw from our observations is that a high concentration of bilirubin in the blood interferes directly with the proper function of the blood-brain barrier. Though the nature of the barrier is unknown, it could be postulated that certain enzyme systems might participate in its maintenance. Physostigmine[24] and SH inhibitors[6] have been shown to increase the permeability of cerebral blood vessels, and it is possible that bilirubin may also act in a similar way as an enzyme inhibitor. This hypothesis could explain the variations in local vulnerability to bilirubin. It is possible that local metabolic pecularities of the brain may modify the function of the blood vessels, as result of which there may be certain differences in the efficiency of the blood-brain barrier from one region to another.

SUMMARY

Permeability of the cerebral blood vessels was studied with radioactive iodinated bovine albumin in newborn rabbits, puppies, and kittens. Under normal conditions, the blood vessels were not permeable to this indicator, though some permeation occurred in the subependymal regions. Twelve- to eighteen-hour hyperbilirubinemia was produced in newborn animals by repeated intravenous injections of a bilirubin-albumin complex. This induced no change of permeability in the rabbits, but, in some of the puppies, a definite increase in the permeability of the gray matter was observed. In kittens, increased permeability developed more commonly than in puppies and was found in the same areas in which the tissue became icteric.

These observations suggest that hyperbilirubinemia may interfere with the proper functioning of the blood-brain barrier. They add further evidence in favor of species differences in the efficiency of the blood-brain barrier. Development of brain damage caused by bilirubin may depend on the degree of this efficiency.

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Headache in childhood

Electroencephalographic evaluation of 500 cases

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James L. O'Leary, M.D., and Herbert E. Rosenbaum, M.D.

BETWEEN 1949 and 1959, a total of 850 children 2 to 15 years old were referred for electroencephalograms because of periodic headache. Of these, 350 were eliminated because organic etiology was suspected. The group does not contain cases referred with the tentative diagnoses of convulsions, mental retardation, subdural hematoma, hydrocephalus, encephalitis, or meningitis, although many of the latter may also have complained of headache. An analysis of our results has value as a population study because of the large size of the group and the importance headache has as a problem in child neurology.

Significantly often, the reason for referral has been the aid expected in ruling out focal cerebral pathology. This is perhaps due to a widespread impression that nonorganic headaches are uncommon in childhood. For example, Holt and McIntosh[1] say that "headaches are not common in little children except in connection with disease of the brain or meninges; in older children they occur from causes similar to those seen in adult life." Senn[2] remarked that "migraine is uncommon in infants and children."

However, migraine as a cause of headache in children has fair acceptance among neurologists. Bramwell[3] estimates that 75% of all cases of migraine become apparent before the age of 20. Hunt[4] found that 50% of a series of cases of "bilious migraine" started before the age of 14. Riley[5] estimated that 2% of children may show an indication of migraine in the first decade. Curschmann[6] concluded that 80% of migraine commences in childhood and thought that too little attention was given childhood migraine in textbooks of either pediatrics or neurology. Krupp and Friedman[7] observed that 35% of 75 children with migraine began complaining of headache before the fourth year.

Sir William Gowers[8] gave the classic description of this malady: "Children are sometimes liable to attacks, probably of the nature of migraine, in which there are severe headaches, fever, and sometimes vomiting. The condition of the child resembles that of one suffering from meningitis, but the symptoms develop more rapidly than those of meningitis, reaching their height in a few hours from the onset. They pass away with equal rapidity. Such attacks may recur at intervals of a few weeks or months. The rapidity of the onset, and the history of previous attacks of the same character distinguish them from more serious affections. Their recognition is important; otherwise you may make a diagnosis of a fatal disease and the patient may be well at your next visit."

For adults, the periodic headache population has been sampled by Ulett, Evans, and O'Leary,[9] who surveyed the electroencephalographic findings of 1,000 adults, excluding traumatic and other organic causes. They found 9.7% of males and 20.5% of females to have clearly disordered tracings. This should be compared with Cohn's[10] series of 824 selected Navy personnel with headache as an isolated "major symptom" showing only slightly more abnormal electroencephalograms (19.9%) than a control group of 251 subjects (14.9%), and Greenblatt's[11] 137 subjects with 35% abnormal electroencephalograms.

The electroencephalogram in migraine of adults has been studied by Strauss and Selinsky,[12] Engel, Ferris, and Romano,[13] Dow and

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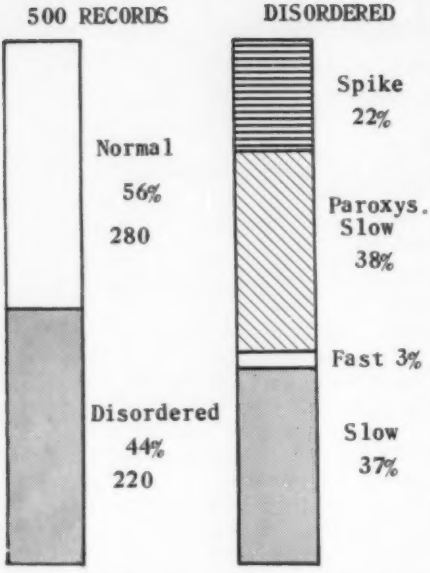

Fig. 1. Histogram comparing percentile groups of disordered and normal tracings (left) and breakdown within the disordered group (right)

Whitty,[14] Weil,[15] and Colony and Stafford.[16] Literature dealing with the electroencephalograms of children with recurring headaches is not as abundant. Michael and Williams[17] report but 1 normal tracing among 11 "migraine" children, while Krupp and Friedman[18] state that electroencephalographic changes were not significant in a series of 50 children with migraine. Livingston[19] studied 62 children with recurrent headaches; 15 (25%) showed disordered electroencephalograms, and, when treated with anticonvulsant drugs, two thirds of the disordered group were much improved. Ziegler and Torres[20] reported a case of focal spike wave activity in a 6-year-old child with headaches but without convulsions.

The fact that, in our laboratory, headache is second only to suspicion of a convulsive disorder as a reason for obtaining electroencephalograms in children is not surprising in view of these selections that have been taken from the literature.

MATERIAL AND METHOD

In a ten-year period, tracings were collected for a total of 850 children ranging in age from 2 to 15 years. The subjects had been referred by physicians because of headaches that occurred in a variety of patterns. Only waking tracings were analyzed, and hyperventilation components were eliminated because of difficulties in assaying them comparatively. Histories, relevant physical findings, and diagnostic impressions were obtained on all outpatients, and the hospital records were inspected on inpatients. The charts of patients who had been hospitalized at St. Louis Children's Hospital were examined before review of the electroencephalographic tracings. The 350 cases were eliminated because of personal history of convulsion, head injury with loss of consciousness or skull fracture, neurologic sequelae of head injury, encephalitis or meningitis, proved or suspected brain tumor, craniostenosis, or mental retardation.

The remainder constitutes our series of children without obvious organic etiology. Electroencephalographic recordings were divided into normal and disordered groups with borderline or other equivocal tracings being included with the normals. The standard of normality used was that of Gibbs and Gibbs.[21] Disordered tracings were classified as slow, paroxysmal slow, paroxysmal spike and fast according to the important activity. Paroxysmal slow records included those showing higher amplitude slow activity of abrupt appearance and disappearance. Records classified as paroxysmal slow and paroxysmal spike graded into each other. Arousal sequences in children were eliminated. In debatable situations, we invariably characterized the questionable formations as paroxysmal slow. Each record was reviewed independently by several readers, and, in the cases of divisions of opinion, the most conservative one was adopted.

RESULTS

The 500 records analyzed derived from 285 males (57%) and 215 females (43%). Of our total population 220 tracings were classified as distinctly disordered, as shown in Figure 1. Of these, the slow disorders accounted for 75% (37% slow, 38% paroxysmal slow). Formations classifiable as spikes (Fig. 2) occurred in 22%

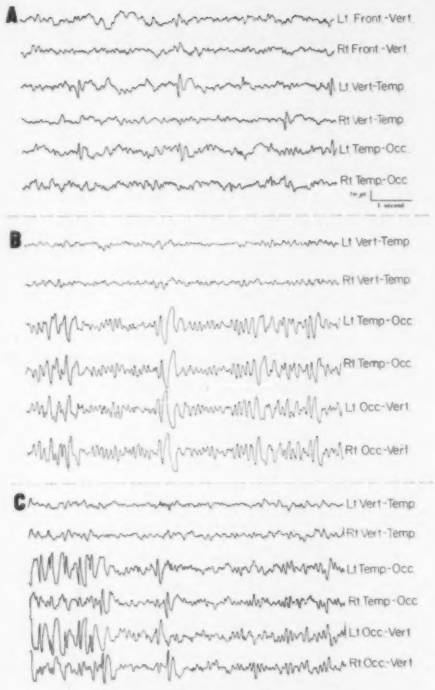

Fig. 2. Tracings from 3 subjects illustrating types of disorder classified as spike dysrhythmias in this series. None had seizure histories. [A] A 7-year-old girl with history of headaches 2 to 3 times per month, of one year's duration. Attacks accompanied by nausea and vomiting and followed by sleep that relieved the headache. [B] A 13-year-old boy who had frontal headaches with nausea and vomiting that lasted for two hours and recurred at three- to four-week intervals. [C] A 7-year-old girl with headaches of throbbing character that recurred 1 to 2 times weekly and were relieved by sleep

of cases, whereas simple fast tracings were found in but 3%. The highest incidence of disorder was evident in those children who were between 5 and 13 years of age, as shown in Figure 3.

In one third of our series, an adequate family history was not available. In another third, there was no family history of migraine or epilepsy. The remainder had a positive family history; 81 children with a family history positive for migraine, epilepsy, or both, showed abnormal tracings, while 78 had normal ones. Thus, between these categories, only a chance difference existed with respect to family history. Familial headache without epilepsy occurred in 61 families of children with disordered tracings as compared with 68 in the normal group. Again, the finding suggested a chance difference. Epilepsy was present in 9 families of the normal group as compared with 10 in the disordered one. The combination of epilepsy and migraine occurred in but 3 families of the normal group as compared with 10 in the disordered group.

The incidence of disordered tracings among males and females did not differ significantly. Of the 215 records from females, 89 (41%) showed disorder. Among 285 tracings from males, 131 (46%) showed disorder.

To determine the incidence of disorder in relation to severity and type of headache, 2 categories were evaluated comparatively. The first included 271 histories of severe headache with phenomena commonly encountered in typical migraine, such as nausea, vomiting, scotomas, blurring of vision, paresthesias, or photophobia. In this group, 139 (51%) had disordered tracings. The second group of 229 cases with history of mild or nonspecific headache and without symptoms associated with migraine syndrome showed 81 (35%) disordered tracings.

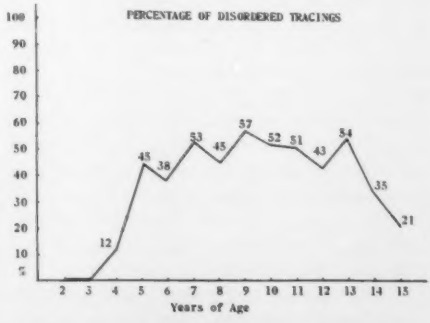

Fig. 3. Graph illustrating the incidence of disordered tracings plotted by age groups. Note that the highest incidence lies between 5 and 13 years.

DISCUSSION

The project was undertaken after it had become apparent that many children who have recurrent headaches have disordered tracings. Our interest was further stimulated by the conflicting medical impression that nonorganic headache is infrequent in the child. We estimate that our 500 tracings of nonorganic etiology were culled from a total ten-year recording of 12,000 to 15,000 children. Thus, 3 to 4% of all children recorded in an electroencephalography laboratory appear to be such subjects.

A diagnostic formulation of the recurring headache problem aids in separating cases with structural disorder from those presenting as precursors of adult migraine. The diagnosis of nonorganic headache in a child requires a history of recurrent headache in conjunction with normal physical examination and roentgenographic findings. A positive family history of recurrent headache may aid; however, this was the case in less than one half of the children in our series. A far more significant datum is the occurrence of earlier episodes of a similar nature and recovery therefrom, although such episodes may not be typically migrainous in pattern. It is also important that significant neurologic or roentgenographic findings weigh heavily in favor of a structural etiology in spite of resemblance to symptoms of migraine.

The reason for the high incidence of disordered tracings in this group of children is conjectural. If the current theory of the pathophysiology of migraine is correct, one might assume broadly that vascular instability somehow relates to the electroencephalographic changes; vascular disturbances have been shown to markedly affect the electroencephalographic pattern by both clinical and experimental laboratory experiences. Such disturbances are nonspecific in character, as are most of the disordered patterns in these patients.

The possibility that the symptom of headache is a convulsive equivalent becomes especially cogent when a classic spike dysrhythmia appears. Such is not unusual when headache and convulsion occur together in a child. For that reason, cases with spike patterns that appear with a negative convulsive history are possible candidates for anticonvulsant therapy. Success with cases showing overt convulsive formations might lead to increased use of anticonvulsants in such cases.

SUMMARY

A survey of 500 children studied at an electroencephalography laboratory over a ten-year period indicates that nonorganic types of headache are not uncommon in children. Our incidence was equally divided between males and females, both of whom had an unusually high percentage of disordered electroencephalograms. The significance of these findings is discussed.

The author's appreciation is extended to Dr. Daniel Holmes for his work in collecting histories from the records of patients from St. Louis Children's Hospital.

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Studies in febrile seizures

V. Clinical and electroencephalographic study in unselected patients

J. Gordon Millichap, M.D., Jack A. Madsen, M.D., and Louis M. Aledort, B.S.

THE SIGNIFICANCE of seizures associated with fever in infants and young children is controversial.[1,2] While some investigators attest to the benign nature and sanguine prognosis of febrile seizures,[3,4] others emphasize the gravity of such symptoms and regard them as evidence of an organic cerebral lesion.[5] In some series of patients, the electroencephalogram was entirely normal and recurrent nonfebrile seizures occurred only in 3 to 5%,[3,4] whereas, in other series, electroencephalographic abnormalities and recurrent nonfebrile seizures were reported in 74 and 31% of patients, respectively.[5,6] These wide variations in statistics may be explained principally by the different criteria employed in selection of cases and by differences in definition of terms.

Prichard and McGreal[7] divide febrile convulsions into two categories, simple and atypical. In studies by Livingston,[3] patients whose seizures are prolonged, focal in type, or associated with electroencephalographic abnormalities are excluded. These are considered "epileptic seizures" in which fever acts as a precipitating factor. The diagnosis of "simple febrile convulsions" is restricted to patients under 6 years of age with short, generalized seizures and a normal electroencephalogram. Similarly, Friderichsen and Melchior[4] omit from their series children with evidence of birth trauma and those with cryptogenic epilepsies.

The relation of febrile convulsions to other epilepsies is widely disputed. Some authors regard them as a specific disorder distinct from the epilepsies, whereas others have used the terms, "mild" or a "pure" form of epilepsy.[1,8] The evidence for a genetic predisposition to febrile seizures is emphasized in support of the specificity of febrile convulsions.

A comprehensive review of the literature by Schmidt and Ward[2] revealed that many of the clinical data were inadequate for purposes of comparison. The need for reports of unselected material was emphasized. The classification of febrile convulsions into subgroups on the basis of the severity of the seizure, electroencephalographic abnormalities, and other criteria is of practical value in the assessment of prognosis. In our understanding of the mechanism of febrile seizures, however, this arbitrary division of cases is confusing.

The purpose of the present study is to present the clinical and electroencephalographic findings in an unselected group of patients seen at a municipal general hospital and to elucidate further the factors of importance in the etiology, mechanism, and prognosis of febrile seizures. Only those patients who attended with febrile seizures during the period of the study were included, so that diagnosis based on retrospective evidence was avoided. Apart from the exclusion of patients with meningitis and infections that involve the brain primarily, a seizure preceded by a significant degree of fever was the only criterion for making the diagnosis.

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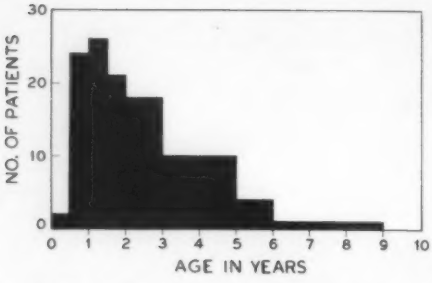

Fig. 1. Age at onset of febrile seizures in 110 patients

MATERIALS AND METHODS

Between July 1956 and June 1958, all infants and children who attended the Emergency Service of the Bronx Municipal Hospital Center with a diagnosis of febrile seizures were referred to the Pediatric Seizure Clinic for complete neurologic study. The data obtained included a personal and family history, physical and neurologic examination, electroencephalogram, roentgenogram of the skull, and blood chemistries. The cerebrospinal fluid was examined at the time of the febrile seizure. At least seven days were allowed to elapse before the electroencephalogram was recorded in order to exclude reversible abnormalities due to the fever per se.[3,9] An 8-channel Grass apparatus was employed, and both monopolar and bipolar records were obtained. The patients were examined at intervals of six months or more frequently, according to the incidence of recurrence of seizures. Those with seizures of long duration and refractory to treatment or with fever that did not respond rapidly to antipyretic measures were admitted to the Pediatric Service.

A record of the following clinical features was made on a check sheet prepared especially for the study: [1] age at onset and frequency of febrile seizures, [2] incidence of recurrence of febrile seizures during a single febrile episode, [3] cause of the febrile illness, [4] height of the fever at the time of the seizure, [5] clinical pattern, localization, and duration of the seizure, [6] occurrence of nonfebrile seizures, and [7] possible etiologic factors other than fever, such as an inherited predisposition to seizures or an acquired brain lesion due to prenatal, natal, or postnatal trauma.

RESULTS

Clinical records were obtained in a total of 110 patients and electroencephalograms in 76 patients.

Sex and race. Febrile seizures were approximately twice as common in boys as in girls; 62% of patients were male and 38% female. The incidence in white, Negro, and Spanish-American races was 53, 26, and 21%, respectively; a similar racial distribution was observed in the general pediatric population at the Bronx Municipal Hospital Center, and the propensity to febrile seizures was not significantly greater in white compared with other races.

Age at onset and frequency of febrile seizures. The first febrile seizure occurred most commonly between 6 months and 3 years of age. An onset before 6 months was observed only in 2 patients and after 5 years, in 6; the latest age of onset was 8 years (Fig. 1).

Febrile seizures had recurred in 58 patients (54%) at the completion of the period of study, and the incidence of recurrence was greater than 4 only in 13 patients (12% of the total), as shown in Figure 2. They recurred as late as 7, 8, and 9 years of age, in 2, 1, and 4 patients, respectively, and with equal frequency

TABLE 1
CAUSES OF 144 FEBRILE EPISODES ASSOCIATED WITH FEBRILE SEIZURES IN 110 PATIENTS

Febrile illness	*Incidence*
	%
Acute tonsillitis or pharyngitis	54
Otitis media	17
Measles	7
Acute bronchitis or pneumonia	6
Gastroenteritis	3
Chickenpox	2
Roseola infantum	1.5
Mumps	1.5
Rubella	0.5
Herpangina	0.5
Unknown	7

TABLE 2
CLINICAL FINDINGS IN PATIENTS WITH FEBRILE SEIZURES UNCOMPLICATED AND COMPLICATED BY NONFEBRILE SEIZURES

Clinical findings	*Febrile seizures alone*		*Febrile and nonfebrile seizures*		*Total patients evaluated*	
		%		%		%
Focal febrile seizures	(11/77)	14	(3/16)	18	(14/93)	15
Prolonged febrile seizures	(8/69)	12*	(5/10)	50*	(13/79)	16
Electroencephalographic seizure discharges	(7/58)	12**	(11/18)	61**	(18/76)	24
Personal history of:						
Prenatal injury		20		27		21
Natal injury		17†		33†		20
Postnatal head injury		15		27		17
Allergy		20		22		20
Recurrent behavior disorder		34		44		35
Recurrent abdominal pain or vomiting		17‡		39‡		21
Family history of:						
Febrile seizures		30		33		30
Nonfebrile seizures		26		39		28
Recurrent seizures		20§		39§		23
Fainting attacks		9		16		10
Migraine		14		16		14
Allergy		35		50		38
Number of patients		77		18		95

Differences significant: *—x^2= 9.5, P<0.01 **—x^2=15.3, P<0.001
Differences not significant: †—P>0.2<0.3 ‡—P>0.05<0.10; §—P>0.1<0.2

in both sexes; 52% of male and 59% of female patients had more than 1 seizure.

In this analysis, a second, third, or fourth seizure within forty-eight hours and in association with a continued fever was included as a single seizure episode; 1 recurrence of this type occurred in 17% of patients and more than 1, in a further 17%.

Cause of fever. A total of 144 febrile episodes was recorded in 110 patients. The causes of the fever and the frequency of their occurrence are shown in Table 1. In the majority of patients, the febrile seizure was associated with acute tonsillitis, pharyngitis, or otitis media. By definition, seizures associated with infections of the central nervous system were not regarded as febrile seizures.

Height of the fever. A body temperature of 38.3° C. (101° F.) or above taken rectally immediately before or at the onset of the seizure was regarded as a significant degree of fever. the mean of 149 recordings of body temperature in 110 children with febrile seizures was 40° C. (104° F.); the range was 38.5 to 41.4° C. (101.2 to 106.5° F.).

Pattern, localization and duration of seizure. A clonic type of seizure pattern was reported in 84% of 96 patients and was associated with a tonic component in 57%. The pattern was principally tonic in only 7% and flaccid or akinetic in 5%. It was not documented in the remainder. Febrile seizures were focal in type in 15%; the incidence of a focal pattern was not significantly greater in patients who subsequently had spontaneous seizures (Table 2).

TABLE 3
RELATION OF LENGTH OF FEBRILE SEIZURE TO INCIDENCE OF NONFEBRILE SEIZURES AND ELECTROENCEPHALOGRAPHIC ABNORMALITIES

Clinical findings	*Duration of febrile seizures*			
	Less than 20 minutes		*More than 20 minutes*	
	Number	*Per cent*	*Number*	*Per cent*
Nonfebrile seizures	5	8*	5	38*
Recurrent seizures	3	5†	4	30†
Electroencephalographic abnormalities	5/48	10§	4/11	36§
Number of patients	66	84	13	16

Significance of differences: *—x^2=9.5, P<0.01
†—x^2=9.3, P<0.01
§—x^2=4.6, P<0.05

The duration of seizures was recorded in 79 patients; the longest seizure in each patient was less than five minutes in 43%, five to ten minutes in 22%, ten to twenty minutes in 19%, and more than twenty minutes in 16%. In 13 patients who had at least 1 febrile seizure that lasted longer than twenty minutes, spontaneous seizures occurred subsequently in 5 (38%) and were recurrent in 4 (30%); the electroencephalogram was abnormal in 36% of patients in this group. The incidence of nonfebrile spontaneous seizures and of seizure discharges in the electroencephalogram was significantly greater in patients with prolonged febrile seizures than in those with seizures that lasted for periods of less than twenty minutes (Table 3).

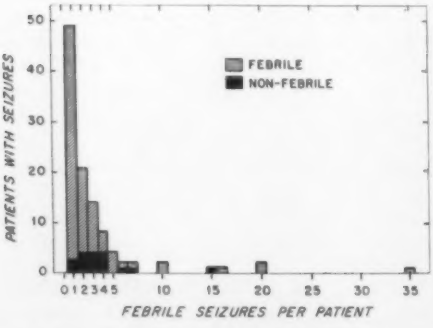

Fig. 2. Frequency of febrile seizures in 110 patients and occurrence of nonfebrile seizures

Incidence of nonfebrile seizures. Spontaneous nonfebrile seizures occurred in 18 (17%) of a total of 107 patients evaluated. The seizures were recurrent in 13 patients (12%), and, of these, 6 had only 1 recurrence, 3 had 5 seizures, and 4 had numerous seizures unassociated with fever. Seizures of the psychomotor type occurred in 1 patient. Figure 2 shows the number of patients with spontaneous seizures in relation to the frequency of recurrence of febrile seizures. In 12 of 18 patients, more than 2 febrile seizures had occurred before onset of spontaneous seizures; in 4 patients, spontaneous seizures anticipated or occurred close to the onset of febrile seizures. The absence of spontaneous seizures in 3 patients who had 20 and 25 recurrences of febrile seizures was exceptional. The average age at onset of nonfebrile seizures was 4 years and that of febrile seizures in the same group of patients was 1½ years. The age at onset of seizures in each of the 18 patients is shown in Figure 3. The clinical findings in patients with febrile seizures alone and in those with nonfebrile seizures in addition are compared in Table 2.

Additional episodic symptoms. Recurrent attacks of disordered behavior were reported in 35% of patients and were manifested by aggression, temper tantrums, and hyperactivity. Recurrent and episodic abdominal pain or vomiting without evidence of visceral pathology occurred in 21%; patients with nonfebrile seizures were affected more commonly than

those with febrile seizures alone, but the difference in incidence was not quite significant (Table 2).

History of possible brain injury. *Prenatal injury.* The following evidence of possible brain injury occurring during the fetal stage of development was obtained in 21% of patients. The frequency of occurrence of each disorder is shown in parentheses: small repeated vaginal hemorrhages during the first and third trimesters of pregnancy (8); toxemia of pregnancy (7); frequent major convulsions in the mother during pregnancy (1); direct trauma to the mother's abdomen (1); rubella and mumps at the fourth month of gestation (2). *Natal injury.* A history of abnormal birth and symptoms suggestive of brain injury were recorded in 20% of patients. One or more of the following abnormalities was possibly contributory: prematurity (8); asphyxia (9); cesarean section (3); breech delivery (2); precipitant birth (1); cord around the neck (1); Rh incompatibility with jaundice and maximal bilirubin level of 5.4 mg. per cent (1). *Postnatal head injury.* Head trauma after birth but before onset of seizures had occurred in 16 patients (17%) and consciousness was lost in 3. Febrile seizures followed trauma of mild degree within twenty-four to seventy-two hours in 5 patients. The higher incidence of possible cerebral injury in patients who subsequently had nonfebrile seizures was not significant (Table 2).

History of allergy. Allergies occurred in 20% of patients as follows: asthma (6); eczema (5); hypersensitivity reactions to orange juice (4), to foods such as wheat, fish, chocolate, and nuts (5), to penicillin (4), to chlortetracycline (1), and to sulfonamides (1). A family history of the following allergies was obtained in 38% of patients: asthma (15); hay fever (8); hypersensitivity reactions to foods including orange juice, chocolate, and veal (4), to penicillin (4), to sulfonamides (1), and to animal hair (1).

Family history of seizures. A history of febrile seizures in near or distant relatives was obtained in 30% of patients, and nonfebrile seizures had occurred in relatives of 28%. Nonfebrile seizures were recurrent in relatives of 23%. A family history of attacks of fainting or migraine was obtained in 10 and 14% of patients, respectively. A predisposition to spontaneous seizures was inherited as frequently as that to febrile seizures and was not significantly more frequent in patients with spontaneous as well as febrile seizures.

Neurologic examination. Abnormalities were found in 20% of patients. These included strabismus (1), Todd's hemiparesis (2), mild hypotonia (3), hyperkinesia (6), retarded motor development (3), and mental retardation (6). Congenital anomalies were present as follows: retrolental fibroplasia (2), Klippel-Feil syndrome and cleft palate (1), and atresia of the auditory canal (1).

Physical development. Height and weight were above the ninetieth percentile in 20 and 13% of patients, respectively; values below the tenth percentile were recorded only in 4%. Measurements were available in 54 patients.

Lumbar puncture was performed in 86 patients, and no abnormality was observed in the cerebrospinal fluid. The concentration of sugar, estimated in all specimens, was greater than 80 mg. per cent in 24 and 100 mg. per cent or higher in 11; abnormally low concentrations were not reported. Patients whose seizures were associated with infectious fevers, such as measles, chickenpox, mumps, and roseola infantum, were examined closely for direct involvement of the central nervous system and signs of encephalitis or meningitis were not observed. *Roentgenograms* of the skull performed in 65 patients were normal in 64; an occipital defect was reported in the patient with Klippel-Feil syndrome.

Blood chemistries were determined within one or two hours of a febrile seizure in a limited number of patients. The level of serum sodium was 130 mEq. per liter or lower in 4

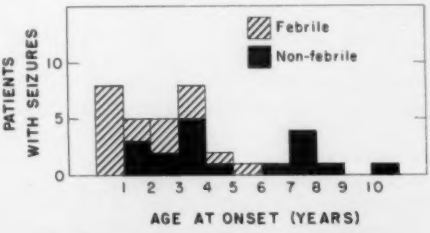

Fig. 3. Age at onset of seizures in 18 patients with both febrile and nonfebrile seizures

TABLE 4
ABNORMALITIES OF THE ELECTROENCEPHALOGRAM IN PATIENTS WITH FEBRILE SEIZURES UNCOMPLICATED AND COMPLICATED BY NONFEBRILE SEIZURES

Electroencephalographic abnormalities	*Febrile seizures alone*	*Febrile and nonfebrile seizures*	*Total patients evaluated*
Centrencephalic	5	8	13
Focal	3	4	7
Paroxysmal discharges:			
Sporadic spikes	1	2	3
Sporadic sharp waves	1	1	2
Sporadic spike and wave		1	1
Rhythmic, 3-per-second spike and wave		2	2
Rhythmic, high voltage slow waves	7	10	17
Rhythmic, 14-per-second positive spikes	1		1
Asymmetry of amplitude	3	1	4
Asymmetry of rhythm	3		3
Exaggerated response to hyperventilation	2	3	5
Number of patients	58	18	76
Patients with seizure discharges	7 (12%)*	11 (61%)*	18 (24%)

*Difference significant: $x^2=15.3$, $P<0.001$

(24%) of 17 patients and 131 to 138 mEq. per liter in the remainder. Calcium, phosphorus, nonprotein nitrogen, and sugar were within normal limits in 5 patients examined.

Electroencephalographic findings. At least 1 electroencephalogram was obtained in each of 76 patients of this series. Some patients had 2 or 3 electroencephalograms, and the total number of records was 89. Sleep and hyperventilation as activating procedures were employed in 52 and 20% of patients, respectively. In the remainder, a study of the response to hyperventilation was precluded by the age of the patient and lack of cooperation.

Normal records were obtained in 52 patients (68%). Abnormalities and the frequency of their occurrence are listed in Table 4. The findings in patients with febrile seizures alone and in those with nonfebrile seizures in addition are compared. Borderline abnormalities found in 6 patients (8%) consisted of minor degrees of slow or fast activity or amplitude asymmetries. Figure 4B shows an example of a borderline record. Paroxysmal high voltage seizure discharges were observed in 18 (24%) and occurred with significantly greater frequency in patients with nonfebrile seizures (61%) than in those with febrile seizures alone (12%). Centrencephalic seizure discharges are shown in Figures 5 and 6 and an example of a focal discharge in Figure 7. In patients with abnormal records, the incidence of focal seizure discharges was not significantly greater in the group complicated by nonfebrile seizures.

The responses to sleep and hyperventilation were tested in 38 and 50%, respectively, of patients whose electroencephalograms were found abnormal and in 56 and 10% of patients with normal or borderline records. The difference in the incidence of sleep records in the 2 groups was not significant, and the more frequent recording of the hyperventilation response in patients with abnormal electroencephalograms could be related to age and a more satisfactory performance of the test. Of 18 patients with seizure discharges in the electroencephalogram, 13 (72%) were 5 to 10 years of age when the record was taken, whereas only 9 (15%) of 58 patients with normal or

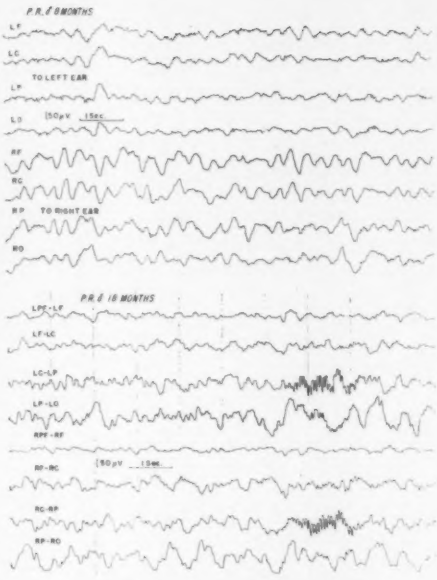

Fig. 4. (P.R.) [A] at 8 months of age: electroencephalogram showing asymmetry with low voltage activity over the left hemisphere and irregular high voltage slow waves on the right. A bipolar record showed the same asymmetry. [B] At 18 months of age: no asymmetry but bursts of 14-per-second, positive spikes in central-parietal leads during sleep. At 8 months of age, the infant had 2 seizures within six hours during fever of 105° F.; no recurrence was reported at 18 months of age. The clonic, focal seizures were confined to the left side. Pregnancy was complicated by toxemia, but birth history and development were normal.

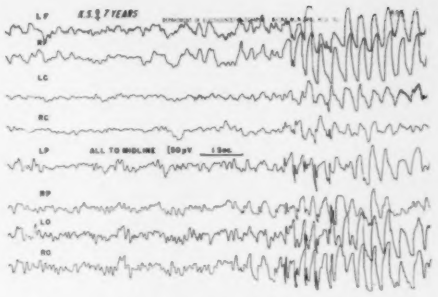

Fig. 5. (K.S.) Electroencephalogram showing centrencephalic-type, spike and slow wave discharge. The patient had 2 seizures with fever of 105 and 106° F. at 9 months and 7½ years of age and 1 seizure without fever at 7 years.

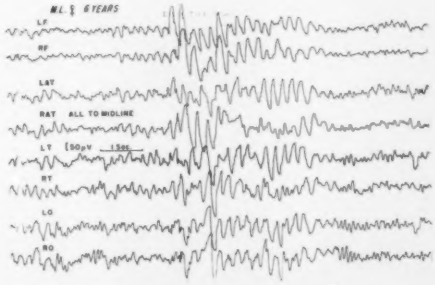

Fig. 6. (M.L.) Electroencephalogram showing centrencephalic-type slow wave discharge. The patient had febrile seizures at 3 months and 6 years of age. The temperature before the second seizure was 104.6° F.

borderline records were in this age group (Fig. 8).

Spontaneous seizures had occurred in 11 patients (61%) with abnormal electroencephalograms and in 7 patients (12%) whose records showed no significant abnormality. The patients with abnormal records were 3 to 10 years of age (average, 7 years) and those with normal records were 1 to 7 years (average, 3 years).

DISCUSSION

Factors concerned in the etiology, mechanism, threshold, and prognosis of febrile seizures will be discussed with reference to the present clinical findings and the results of previous laboratory studies.[10–12]

Etiology, mechanism, and threshold. *Fever.* The recognition of fever at the onset of a convulsion is a sine qua non in the diagnosis of febrile seizures. In laboratory animals with induced hyperthermia and in children with infection, the height of the body temperature was the essential factor in the etiology of febrile seizures.[10] In the present study, some children with a low seizure threshold convulsed with fever of 38.3° C. (101° F.), whereas others with a high threshold had seizures

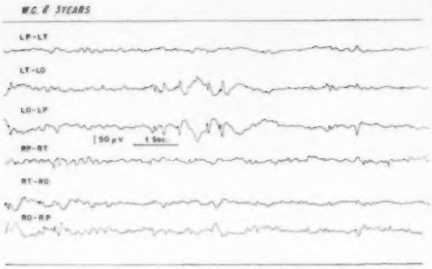

Fig. 7. (W.C.) Electroencephalogram showing spike and slow wave focus with phase reversal in left occipital area. A moderately retarded boy with retrolental fibroplasia. He had 3 seizures with fever higher than 102° F. between 2 and 3 years of age, each of which lasted one-half to one hour and 1 of which was focal with onset in the right arm; 2 generalized convulsions occurred subsequently without fever at 3½ and 4 years of age.

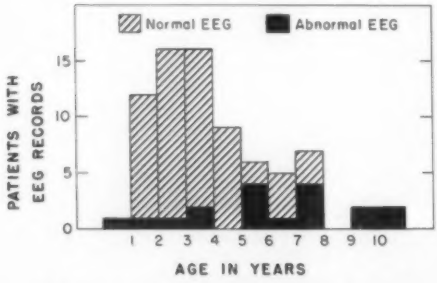

Fig. 8. Age at the time of electroencephalographic recording in 76 patients with febrile seizures. Abnormal records are those with recurrent and paroxysmal seizure discharges.

when the body temperature was 41.4° C. (106.5° F.).

In animals, the threshold convulsive temperature varied with age and the maturation of the balance of water and electrolytes in the brain,[11] but, apart from rats aged 3 to 7 days which convulsed at relatively low body temperatures, the seizure threshold was considerably higher than that of children. The disparity between the mean values of the convulsive temperature observed in children and in animals may be explained by differences in degree of maturation or by a lowered threshold to febrile seizures in children, which is frequently inherited. Further, the source of fever may be important; in children with infection, a factor in addition to the degree of hyperthermia may be involved in the seizure mechanism.

Infection. The significance of infection in the etiology of febrile seizures is difficult to assess. It has been suggested that the brain is involved directly in infections such as roseola infantum (exanthema subitum)[13] and that a generalized alteration in the permeability of cell membranes and capillaries with cerebral damage may result from the toxic products of other infections.[14] As in other series of patients, we have found that febrile seizures occur most commonly with acute infection of the upper respiratory tract.[3,4,15] The frequency of association with acute tonsillitis, pharyngitis, and otitis media may be explained by the prevalence of these infections in young children between the ages of 1 and 3 years. Roseola infantum was the cause of fever in only 2 of our patients; the cerebrospinal fluid was normal, and there was no evidence of an encephalitic process. Our findings agree with those of Livingston,[3] and, without more specific indications of direct cerebral involvement, the relative frequency of febrile seizures in patients with roseola infantum may be explained by the consistently high fever found with this infection.

Allergy. That hypersensitivity reactions may be important in the initiation of seizures in some patients is suggested by the relatively high incidence of allergic symptoms in our patients and their relatives. Immune reactions to the toxic products of infecting organisms[14] may occur, and the patient may be allergic to penicillin, aspirin, and other agents used in the treatment of the febrile illness. The role of histamine and allergy in the initiation of the seizure discharge has been discussed in a previous communication.[16]

Water and electrolyte imbalance. The threshold to febrile seizures may be lowered in animals by the experimental induction of hyponatremia, and low levels of serum sodium have been observed in close relation to the occurrence of febrile seizures in children.[11] In patients susceptible to febrile seizures, the

hazards of water intoxication[17] should be emphasized and the rapid administration of hypotonic parenteral solutions during acute febrile episodes should be avoided.

Carbonic anhydrase that catalyzes the hydration and dehydration of carbon dioxide is intimately involved in the metabolism of water and electrolytes in the brain. The enzyme appears to be essential for the propagation and generalization of a seizure discharge;[18] its activity in the brain is directly related to the development of susceptibility to various seizure patterns in the young.[19] Infants have relatively low levels of carbonic anhydrase in the brain,[20] and their threshold to seizures is high compared with children of 4 to 8 years of age, who are most susceptible to cryptogenic epilepsies.[3,18] Since enzyme activity is accelerated by a rise in body temperature, however, it might be expected that susceptibility to febrile seizures would develop at an earlier age than that to spontaneous seizures.

Age. Febrile seizures occur most commonly between 6 months and 5 years of age. An onset before 3 months and a recurrence after 9 years was not observed in the present study. Laboratory experiments suggest that the high threshold to seizures in the newborn is related to a low concentration of carbonic anhydrase and a reciprocal high level of carbon dioxide in the brain,[21] whereas the resistance to febrile seizures in older children and adults may be due to changes in the balance of water and electrolytes with maturation[11] and the possible development of enzyme systems that inhibit the seizure discharge. The increased susceptibility of young compared with adult rats has been correlated with the developmental changes in the ratio of intracellular to extracellular cations in the brain.

An alternative or additional but less plausible explanation for the predilection of the febrile seizure for the young is the increased exposure and susceptibility to upper respiratory tract infection at this age. However, the almost complete absence of seizures of this type in children more than 10 years of age would militate against this theory.

Sex. The influence of sex on the susceptibility to febrile seizures is dicussed by W. Lennox.[1] In the present series of patients and in that of M. Lennox,[22] males were affected twice as commonly as females. An increased liability to congenital defects and birth injuries has been postulated as a possible explanation for the high incidence of lowered seizure threshold in the male.

Heredity. In contrast to a number of previous reports,[1,3,7] evidence for an inherited predisposition to febrile seizures, obtained in one third of patients of this series, was equally strong in those who suffered from nonfebrile seizures in addition. Further, a tendency to nonfebrile seizures was inherited no less frequently than that to febrile seizures. It is suggested, therefore, that the genetically determined abnormality that may result in a low threshold to febrile seizures is of the same nature as that which may underlie susceptibility to spontaneous seizures in some patients. In febrile states, the tendency to seizures is enhanced and is manifested at an earlier age.

In our understanding of the mechanism of seizures, therefore, a distinction between febrile seizures and the epilepsies is unjustified on the basis of genetic evidence obtained in the present study. It is admitted, however, that a number of authors have reported a genetic predisposition to febrile seizures in a greater proportion of patients. Our data contrast with these observations, and our conclusions are similar to those of W. Lennox,[1] who regards the febrile seizure as an epilepsy.

Acquired brain injury. In patients with a tendency to seizures acquired factors may also be important in etiology. Bridge[23] and Peterman[5] emphasize the organic basis for febrile seizures. Indeed, Peterman states that a febrile convulsion is a symptom of an organic cerebral lesion precipitated by an elevated body temperature. In a study by W. Lennox,[1] however, evidence of antecedent cerebral pathology was found less frequently in patients whose initial seizures were febrile than in those who presented with spontaneous seizures. Nevertheless, in the present series of patients, a history of birth trauma was obtained in 20%. In children who subsequently had nonfebrile seizures, the incidence of trauma was twice that found in the group with febrile seizures alone, but the difference was not significant.

It seems, therefore, that the threshold to febrile seizures may be lowered by an inherited and functional cerebral defect or by ac-

quired and structural lesions of the brain. With cryptogenic seizures, prognosis is good; with acquired brain pathology, the seizures are more severe and persistent.

Prognosis. *Recurrence of seizures.* The incidence of recurrence of febrile seizures in the present series of patients was approximately the same as that observed in studies of much longer duration.[1,3] Febrile seizures are likely to recur in 50 to 60% of patients, but only 10 to 20% will have more than 4 seizures.

During a single febrile episode, the chance of seizure recurrence was about 1 in 3, an incidence somewhat higher than that reported by other workers. The patients were admitted to the ward because of continuous fever refractory to antipyretic therapy. Wegman[24] has emphasized the importance of a rapid rise in temperature at onset of infection in the mechanism of febrile seizures, but the present data belie this conception. In addition, laboratory studies have shown that, in animals subjected to febrile seizures, a postictal elevation in threshold occurs.[12] Thus, a higher body temperature would be needed to induce a second seizure, and the infrequent recurrence despite continued fever may be explained.

Spontaneous nonfebrile seizures. Apart from rare postictal paralysis, the most serious complication of febrile seizures is the occurrence of seizures without fever. In patients reviewed by W. Lennox,[1] the interval between febrile seizures and the onset of spontaneous seizures varied from one month to thirty-five years and was less than one year in 53% of patients; nonfebrile seizures were first to occur in 6%. The follow-up period in the present study ranged from six months to two years with an average of twelve months, and the proportion of patients with nonfebrile seizures is probably lower than expected in an unselected group.

At the completion of the study, spontaneous seizures had occurred in 17% of patients; they were recurrent in 12% and frequent in only 4%. Approximately the same incidence of nonfebrile seizures is reported by Buchanan[25] and Zellweger.[26] An analysis of the literature reveals that the assessment of prognosis by other investigators is similar when allowance is made for selection of cases and the term epilepsy is used to define either a single or frequent recurrence of nonfebrile seizures. W. Lennox[1] reports subsequent spontaneous seizures in 77% of patients but stresses the limitations of retrospective studies in which a high proportion of adult patients with chronic epilepsies is included. He concludes that less than 5% of children whose initial seizure is fever-induced may later have spontaneous seizures. Friderichsen and Melchior[4] diagnose epilepsy in 3% of patients in a selected series but admit to the subsequent occurrence of nonfebrile convulsions in 20%. Thus, the extreme disparity in reports by various authors may be reconciled; in an unselected group of patients with febrile seizures, convulsions without fever may be expected in approximately 20% and may recur frequently in 5%. A higher percentage of patients may be affected when less overt forms of seizure activity are included.

With respect to the patterns of subsequent seizures, an undue proportion of patients with psychomotor seizures is reported by W. Lennox,[1] which suggests that febrile seizures may sometimes be attended by temporal lobe lesions. Of patients in the present study, only 1 had typical psychomotor-type seizures, but recurrent and paroxysmal behavior disturbance occurred in 35%. The frequent history of periodic attacks of abdominal pain and vomiting without evidence of visceral pathology was suggestive of an autonomic or diencephalic seizure disorder.[27] A centrencephalic type of abnormality was found in 65% of patients with seizure discharges in the electroencephalogram, and the probable involvement of subcortical structures in febrile seizures, as suggested by Schmidt and Ward,[2] is supported.

Abnormalities in the electroencephalogram and febrile seizures of long duration were the principal criteria indicative of a poor prognosis. In contrast to previous reports,[3,28] the occurrence of focal febrile seizures was unrelated to the development of nonfebrile seizures. Descriptions of patterns of seizures, even by medical observers, may be unreliable, but the absence of spontaneous seizures in a number of patients with focal abnormalities in the electroencephalogram limits the significance of this factor in assessing prognosis.

In patients with 1, 2, and 3 recurrences of febrile seizures, the incidence of spontaneous seizures was directly related to the frequency of febrile seizures. Conventional anticonvul-

sant drugs are of doubtful value in the treatment of fever-induced seizures[12] but may have been responsible for the failure of spontaneous seizures to develop in 3 patients who had 20 and 35 recurrences with fever.

The harmfulness of convulsions associated with fever is emphasized in some reports,[15,29] and the occurrence of nonfebrile seizures has been attributed to brain injury sustained during an initial febrile convulsion. That hyperpyrexia with prolonged convulsions may result in neuronal necrosis and permanent brain damage is well known. Present evidence suggests, however, that febrile seizures generally do not predispose to spontaneous seizures but that this complication is dependent upon genetic or acquired etiologic factors that are common to both types of seizures.

SUMMARY

In an unselected group of 110 patients with febrile seizures, nonfebrile seizures occurred in 17%, recurred in 12%, and were frequent in 4%. Recurrent attacks of abdominal pain and vomiting in 21% suggested a concomitant autonomic seizure disorder. Psychomotor seizures occurred only in 1 patient, but episodic behavior disturbance was reported in 35% of patients. Seizure discharges in the electroencephalogram were observed in 24% of 76 patients tested.

The etiology and mechanism of febrile seizures are dependent upon a rise in body temperature in a patient with a low threshold to seizures. Fever accelerates metabolic processes that facilitate the spread of a seizure discharge. Toxic products of infecting organisms, hypersensitivity to certain allergens, and electrolyte imbalance may be contributory.

The height of the body temperature at which a seizure occurs is an index of the febrile seizure threshold. Age, immaturity of cerebral electrolyte balance, sex, heredity, and acquired brain pathology are important determinants of a low threshold to febrile seizures.

A tendency to nonfebrile seizures appears to be dependent upon the same hereditary and acquired factors as those important in febrile seizures.

The authors wish to thank Miss Molly Cox for the electroencephalographic recordings.

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Differentiation of tumors arising in area of the posterior third ventricle

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TUMORS arising in the region of the posterior third ventricle present an unusual problem to the clinician since current methods of treatment preclude direct visualization of these growths and the reassuring microscopic confirmation of their cell type.[1–3] Although examples of successful removal of pinealomas have been recorded,[4–8] it was found some time ago that direct attack upon tumors in this region was usually disastrous. Most surgeons have felt obliged, therefore, to content themselves with temporizing measures such as third ventriculostomy, ventriculocisternostomy, or subtemporal decompression, seeking more durable effects from radiotherapy.[1–3] Since pinealomas are relatively sensitive, this form of treatment has been, by and large, successful.

However, infiltrating gliomas also appear in this region, which, from the standpoint of their ventriculographic appearance, may be indistinguishable from the pinealomas. These tumors progressively infiltrate the brain stem and, not being particularly radiosensitive, may cause death within a few months in spite of the above measures.

At the present time, then, there is little to offer patients with infiltrating gliomas of this region. They would, however, derive some benefit from a more accurate appraisal, and radiation therapy, with the prolonged hospitalization it necessitates, could be avoided.

In addition, patients with papilledema and cerebellar signs have often undergone posterior fossa explorations because of ventriculographic evidence of dilated lateral and third ventricles with nonvisualization of the cerebral aqueduct and fourth ventricle.[3,4] Some time later, they are found to have neoplasms infiltrating the cerebral aqueduct. Careful clinical assessment might more accurately localize these tumors, thereby obviating cerebellar exploration.

We have compared two groups of patients, one with pinealomas and the other with gliomas in the region of the posterior third ventricle, and have attempted to differentiate one group from the other on the basis of neurologic findings alone, as they relate to the involvement of various functional components in the underlying brain stem.

ANATOMY

Fibers responsible for following upward movements of the eyes are carried in the internal corticotectal tract that passes from areas 18 and 19 of the occipital and preoccipital cortices to the anteriomedial and medial portions of the superior colliculi, as demonstrated in Figure 1. Here, they synapse with tectooculomotor fibers that descend to that part of the oculomotor nucleus that is responsible for following conjugate movements of the eyes above the plane of the horizon. Impulses mediating following conjugate movements of the eyes in the downward direction discharge through the same pathway but end in the posterolateral portions of the superior colliculi.

The corticobulbar tracts mediating voluntary upward and downward movements of the eyes are also shown in Figure 1. They descend from the frontal motor eye fields and, at superior collicular levels, turn off from the cerebral peduncle into the tegmentum of the midbrain to synapse in the contralateral and ipsilateral oculomotor nuclei.

Fibers contributing tonicity to upward gaze, and probably to other directions of gaze as well, ascend in the flocculooculomotor component of the superior cerebellar peduncle in

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the tegmentum of the midbrain from the flocculus of the cerebellum to the third nerve nucleus.

Theoretically, then, one should be able to distinguish three components of upward gaze, and a defect in any one should be localizing. Clinically, however, it is virtually impossible to make this differentiation.

Figure 2 diagrams the fibers from the retina responsible for the pupillary reaction to light, which are relayed through the optic nerves and tracts to the pretectal nuclei located immediately below and just in front of the superior colliculi. Here, synapse is made with fibers that descend to the Edinger-Westphal nucleus. This last mentioned nucleus provides a preganglionic component of the third nerve which mediates constriction of the pupil by way of the ciliary ganglion.

The superior cerebellar peduncle arises chiefly from the dentate nucleus and ascends in the tegmentum of the midbrain, where it decussates at inferior collicular levels just before it reaches the red nucleus (Fig. 3). After synapsing in part with the red nucleus, it continues superiorly to the nucleus ventralis lateralis of the thalamus. Here, synapses are made with fibers that extend to areas 4 and 6 of the cerebral cortex by way of the posterior limb of the internal capsule. Involvement of this tract anywhere along its course will produce signs of cerebellar dysfunction.

Pathways concerned with wakefulness and, possibly, emotional expression arise in the caudal hypothalamus and descend as the dorsal and posterior hypothalamotegmental tracts to superior collicular levels, where they end in the tegmental gray above and below the red nucleus. Figure 4 demonstrates this pathway. Emotional expression may also be influenced by the dorsal longitudinal fasciculus, which arises from almost all nuclei of the hypothalamus and descends in the periaqueductal region of the brain stem to terminate on the various motor nuclei of the cranial nerves. Direct corticotegmental tracts from the various cortical areas, including temporal lobe and cingulate gyrus, also discharge to the red nucleus and the deep tegmental gray adjacent to it. These systems play a part in emotional expression as well as serving to supplement various pyramidal tract activities.

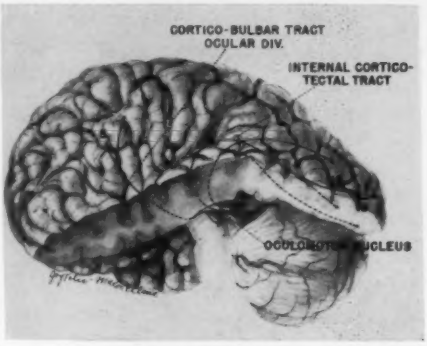

Fig. 1. Pathways responsible for following and voluntary movements of the eyes in the upward direction

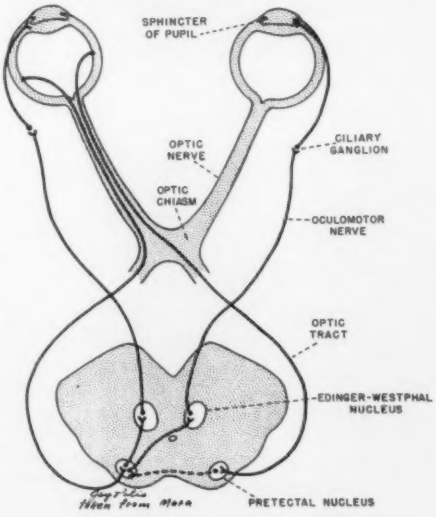

Fig. 2. Fibers mediating the pupillary reaction to light

CLINICAL MATERIAL

For the purpose of investigation, we selected 35 patients from the Neurosurgical Service at the University of Michigan Hospital, all of whom had neoplasms arising from the posterior third ventricle (Fig. 5). Unfortunately, microscopic confirmation of tumor type was not obtained in all cases since, in recent years, the treatment of choice at this institution has become ventriculocisternostomy or subtempo-

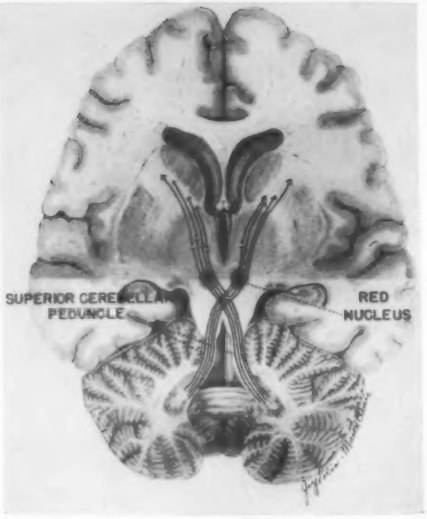

Fig. 3. The superior cerebellar peduncle

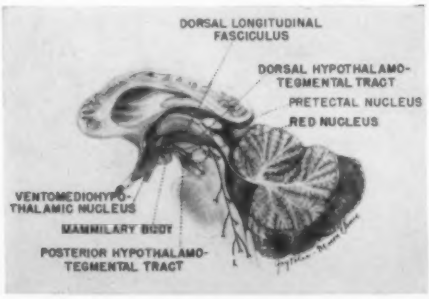

Fig. 4. Pathways concerned with wakefulness and, possibly, emotional expression

ral decompression with or without irradiation.

Pinealoma was diagnosed in 17 patients and confirmed microscopically in 10, 7 having pinealomas and 3 having pinealoblastomas. Another 7 patients were presumed to have pinealomas, since 6 are still alive five to fifteen years after surgical treatment with irradiation; 1 was lost to follow-up after four years.

Gliomas of the posterior third ventricle were verified microscopically in 18 patients; 10 had astrocytomas, 3 glioblastomas multiforme, and 4 spongioblastomas polare, and, in 1 patient, the type of glioma could not be determined.

Papilledema figured equally prominently, being found in roughly three fourths of both groups of patients in this series. In most cases, this finding was attributed to obstruction of the cerebral aqueduct. It does not serve as a distinguishing feature between the two groups.

Since fibers mediating following gaze in the upward direction synapse in the superior colliculus and those responsible for voluntary upward gaze descend in the tegmentum of the midbrain, careful attention to the component of upward gaze affected should aid considerably in differentiating pinealomas from gliomas of the posterior third ventricle. Pinealomas, by compressing the superior colliculus, should cause a loss of following upward gaze, the voluntary component remaining intact, but gliomas of the posterior third ventricle should cause the reverse, since they often begin in the mesencephalic tegmentum.

It was, however, impossible to distinguish by this means between the 2 groups of patients in the present series. In the first place, only 53% of the patients with pinealomas showed any loss of upward gaze and in only 44% of those with gliomas of the posterior third ventricle was this finding evident. In the second place, in the earlier cases, no attempt was made to define the component of upward gaze lost. In later years, however, differentiation still could not be made.

Loss of the pupillary reflex to light was the most constant finding in patients with pinealomas, being evident in 82%. In most cases, this sign was attributed to involvement of the pretectal nucleus lying just beneath the superior colliculus. Of the patients with gliomas, 67% had this finding, which was believed to result more from extension of the tumor into the Edinger-Westphal component of the third nerve nucleus than from its effect on the pretectal nucleus. This assumption is perhaps strengthened by an incidence of 56% of other signs of third nerve involvement in this group. Only 35% of the patients with pinealomas had third nerve findings which, in most of them, were probably secondary pressure effects.

No differentiation between pinealomas and gliomas of the posterior third ventricle could be made on the basis of other cranial nerve abnormalities, since these were found in slightly less than half of the patients in both groups.

On the other hand, only 35% of the patients with pinealomas showed pyramidal tract signs, compared to an incidence of 61% in the glioma group. Only 18% of the former had cerebellar signs, whereas 72% of the patients with gliomas had findings suggesting cerebellar impairment. Only 29% of the patients with pinealomas had mental changes, chiefly somnolence. In contrast, similar abnormalities were observed in 78% of the patients with gliomas.

These 3 findings, then—pyramidal tract involvement, cerebellar abnormalities, and mental changes—constituted the chief means of distinguishing between the patients.

It should be mentioned that 5 patients with pinealomas had papilledema and little else. Except for a sixth nerve paresis in 1 patient, 3 of them had no other findings. The other 2 had, in addition, loss of pupillary light reflex. On the other hand, all patients with gliomas of the posterior third ventricle had pronounced neurologic findings when first seen.

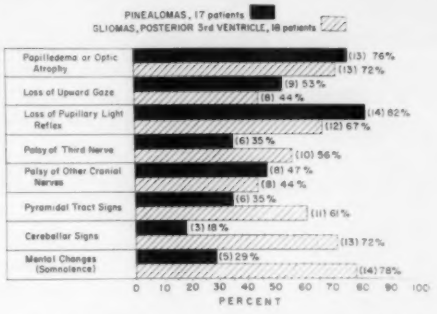

Fig. 5 Comparison of signs in patients having pinealomas with those in patients with gliomas of the posterior third ventricle

CONCLUSIONS

1] Loss of the pupillary reaction to light in the absence of optic atrophy but in the presence of signs of increased intracranial pressure suggests a mass in the posterior third ventricle. If upward gaze is also lost, localization to this region is virtually confirmed.

2] Ventriculographic evidence of a posterior third ventricular tumor in a patient with minimal clinical findings suggests pinealoma rather than glioma.

3] Gliomas of the posterior third ventricle tend to infiltrate the midbrain tegmentum before they have grown sufficiently to obstruct the ventricular system. Patients with gliomas, therefore, commonly present pronounced neurologic findings, specifically, signs of third nerve involvement, pyramidal tract abnormalities, cerebellar dysfunction, and mental changes in addition to loss of the pupillary light reflex and, perhaps, upward gaze. Papilledema, although usually present, does not constitute the major clinical finding.

4] Ventriculographic evidence of internal hydrocephalus with nonvisualization of the cerebral aqueduct and fourth ventricle suggests the presence of a posterior fossa tumor in patients with papilledema and signs of cerebellar dysfunction. However, loss of the pupillary light reflex or upward gaze or signs of third nerve impairment incriminate the posterior third ventricle. Pneumoencephalography may confirm this localization, and posterior fossa exploration becomes unnecessary.

SUMMARY

1] The anatomic relations of the posterior third ventricle have been reviewed in reference to tumors arising in this region.

2] A series of 35 patients with tumors of the posterior third ventricle is presented, and an attempt is made to differentiate clinically between pinealomas and gliomas of the posterior third ventricle.

3] Differentiating between the two would seem justified.

The author is indebted to Dr. Elizabeth C. Crosby for her guidance and help with the regional neuroanatomy and to Dr. Edgar A. Kahn for his comments and suggestions pertaining to the text, as well as for the privilege of utilizing the clinical material.

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Guillain-Barré syndrome resulting from tetanus antitoxin injection

Second reported case with immunologic studies

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GUILLAIN-BARRÉ syndrome is a rare sequela of serum disease. Cases with paralysis but without detailed serologic studies have been reported intermittently since 1929. However, it was not until 1958, when Arbesman and associates[1] reported such a patient, that this syndrome received serologic study.

The patient had Guillain-Barré syndrome after serum disease due to tetanus antitoxin and was shown to have hemagglutinating and other antibodies in high titer in blood and spinal fluid. The case report and detailed serologic studies suggested tetanus antitoxin as the etiologic agent and an immunologic or some allergic mechanism as the pathogenic process.

Guillain-Barré syndrome also has been occasionally reported after smallpox vaccination.[2] An early report[3] described various neurologic complications attributed to human antiserum, and an article[4] appearing later warned particularly of peripheral nerve paralysis after injections of various antiserums, tetanus antitoxin being the principal offender.

This syndrome of polyradiculoneuritis with albuminocytologic dissociation has been known since 1916.[5] Before the present name, Guillain-Barré, became widely accepted, the entity was considered to be acute infective polyneuritis[6] by those who first saw it in England and as infectious neuronitis[7] in the United States. It has been described[8] as an inflammatory process that involves the spinal nerves and extends for a short distance proximally and distally to cause varying degrees of motor and sensory derangement. A mild antecedent infection, usually of the upper respiratory tract, was considered a possible etiologic factor. The symptomatology ranges from mild temporary disturbances to a fatal ascending paralysis.[9-19]

We are reporting a patient, studied immunologically and clinically, who exhibited Guillain-Barré syndrome after tetanus antitoxin serum disease, because the findings are similar in many respects to Arbesman's case (Table 1), tending to confirm his incrimination of at least one etiologic agent for the diseases included in this syndrome. Our patient's course was typical for Guillain-Barré syndrome, and she exhibited hemagglutinating antibodies in her serum which persisted for a long time.

CASE REPORT

H. M., a 37-year-old white housewife, ran a rusty nail into her left hand on July 24, 1958. The wound was cleansed, and she was given 0.5 cc. of undiluted tetanus antitoxin after a skin test revealed only a suggestion of erythema. Several hours after the injection, she had a chill and fever but was otherwise well until four days later, when chills and fever recurred along with joint pains and swelling in the left shoulder, the site of the injection.

She was admitted to the South Unit of the Youngstown Hospital Association on July 31, one week after her accident, because of progressive weakness of the lower extremities. She was unable to walk. She also complained of pain in the back, numbness of the hands and face, and a feeling of heaviness in both arms.

From the Youngstown (Ohio) Hospital Association and the Buffalo (N. Y.) General Hospital.

TABLE 1

SPINAL FLUID FINDINGS COMPARED WITH CASE OF ARBESMAN AND ASSOCIATES[1]

Days after tetanus antitoxin	Arbesman and associates		Present case	
	White blood cells	Protein mg. per 100 cc.	White blood cells	Protein mg. per 100 cc.
9	–	–	4	200
14	7	290	0	150
18	–	–	2	75
23	8	260	0	100
31	10	174	–	–
40	–	–	0	55
99	4	45	–	–

The patient had received tetanus antitoxin at age 6 or 7 without a reaction. She had had an appendectomy in 1954. Penicillin had been given intermittently over a period of years for chronic otitis media, but the drug was discontinued in June 1957, when she had a mild skin rash after a penicillin injection. She was also allergic to pork. No other evidence of allergy was obtained. There was no family history of allergies.

Physical examination on admission showed temperature, 98.6° F.; pulse, 85; and respirations, 18 per minute. She did not appear in acute distress. Positive findings included slight nuchal resistance, shallow respiratory movements, and absent abdominal and deep tendon reflexes; the plantar reflexes were diminished but flexor. The peripheral blood count on admission showed 4,540,000 red blood cells per cubic millimeter, hemoglobin of 13.8 gm., and hematocrit of 44%. The white blood count was 8,000: polymorphonuclear forms, 69; stabs, 5; lymphocytes, 25; and monocytes, 1. Urinalysis was negative. A VDRL test for syphilis was negative. She was started on 5 mg. of Meticorten four times daily and barbiturate sedation when needed.

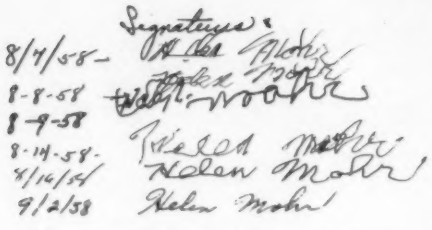
On the second day, she was apprehensive, nervous, and crying; she complained of headache, backache, and cramps, the last associated with her menses. She also had some hesitancy in speaking, but her words were clear. Left peripheral facial palsy, profound lower extremity weakness, and diffuse slight weakness of the upper extremities were demonstrated. Pain and vibratory senses were intact, but position sense was gone in both big toes. Blood cultures were done anaerobically to rule out tetanus, although there was no evidence for an active clostridial infection.

On the fourth hospital day, a lumbar puncture demonstrated colorless fluid at an opening pressure of 240 mm. of water. After 12 cc. was removed, the pressure was 150 mm; 4 lymphocytes and a protein concentration of 200 mg. per 100 cc. of spinal fluid were found.

On the fifth hospital day, she had less leg weakness but complained of numbness of the tongue and said her arms were very heavy. She choked when sipping water or attempting to swallow medications. Respirations remained normal. Her words were badly slurred. Flattening of the nasolabial folds, which gave a blank expression to her face, was noted. She also complained of some blurring of vision in the left eye, but no diplopia or anisocoria was noted and the funduscopic examination was negative. That evening, she expectorated a large amount of thick, tenacious mucus and, after this, had no further difficulty taking sips of water or medications.

By the seventh hospital day, the patient's apprehension was lessened and she was able to talk clearly for the first time and to write her name (see illustration); nevertheless, occasionally, she was incoherent, mumbled to herself, and expressed fear that the personnel were going to do things to hurt her.

On the ninth day, a second lumbar puncture revealed a protein of 150 mg. per cent with no cells. On the tenth day, she sat briefly in a chair. Her lower limbs remained paralyzed, and her upper limbs were then at their weak-



Examples of patient's signature made during the course of her illness

est. A lumbar puncture on the thirteenth hospital day showed a protein of 75 mg. per 100 cc. By the fourteenth day, she had regained some hand strength, although she was bothered by severe leg cramps. She was able to turn herself in bed for the first time on the fifteenth day. On the nineteenth day, the spinal fluid protein was 100 mg. per 100 cc. with no cells. Return of leg power was sufficient by the next day to allow the patient to use a walker briefly. Formal physical therapy aimed at better return of small muscle function was started on August 26. The last lumbar puncture was done on September 4 and showed a protein of 55 mg. per cent without cells. On September 5, she was able to walk unaided, although toe movement had not entirely returned and there was some residual weakness. She was discharged from the hospital on September 6, able to use her hands normally.

Follow-up neurologic examination on December 30, 1958, revealed numbness of the small toe on the left foot and weakness of triceps, deltoid, and gluteal muscles bilaterally as her only sequelae. When seen again on March 13, 1959, the gluteal strength had become normal and deltoid and triceps had improved.

A specimen of her serum obtained on the one hundred fifty-third hospital day showed hemagglutinins to horse serum in a titer of 1:32,000. (Human type O, Rh-negative red blood cells were washed 3 times with buffered saline, resuspended to 2%, and incubated at 37° C. with 1:20,000 tannic acid. After washing, the cells were again suspended and incubated at room temperature with horse serum and saline. The sensitized red blood cells were resuspended to their original volume, and 0.05 cc. was added to the antiserum to be tested. The antiserum was serially diluted in *p*H 7.2 buffered saline. Controls consisted of normal human serum and normal rabbit serum with coated red blood cells, as well as antiserum with uncoated tanned cells.)[20] A second specimen obtained on the two hundred and twenty-second day showed a titer of 1:12,000 (Table 2). Precipitins, anaphylaxis, and Prausnitz-Kustner antibodies on two recipients could not be demonstrated.

DISCUSSION

The diagnosis of Guillain-Barré syndrome would appear to be sound in our patient. The presence of hemagglutinins in extremely high titer would indicate that hypersensitivity to horse serum played a role in the etiology of this case.

The very striking antibody response to a relatively small dose of antiserum may be related to the fact that this patient had received antiserum at the age of 6 or 7, some thirty years previously.

Guillain-Barré syndrome (acute idiopathic polyneuritis, Landry's paralysis, acute infective neuronitis) until very recently has been considered a disease of undetermined etiology. Sporadic reports have appeared in the medical literature from time to time suggesting various etiologic agents, but, recently, an allergic mechanism has been suggested on the basis of experimental data.[21] The two cases referred to in this report, while not establishing the etiology for all cases of Guillain-Barré syndrome, certainly suggest a hyperimmune response to

TABLE 2

HEMAGGLUTINATION CAUSED BY PATIENT'S SERUM (TITERS*)

Days after tetanus antitoxin	*Arbesman and associates*	*Present case*
16	5,000,000	–
31	5,000,000	–
69	320,000	–
97	640,000	–
156	160,000	32,000
222	–	12,000

*Reciprocal of highest dilution of patients' serum producing agglutination of red blood cells coated with horse serum.

horse serum as the causative agent for at least this segment of cases.

SUMMARY

1. We have presented what we believe to be the second patient with Guillain-Barré syndrome resulting from tetanus antitoxin injection in whom detailed serologic studies were carried out.

2. Hemagglutinating antibodies against horse serum were demonstrated after the injection of tetanus antitoxin.

3. The antibodies persisted for at least two hundred and twenty-two days.

4. The presence of hemagglutinins against horse serum in extremely high titer would suggest that hypersensitivity to horse serum played a role in the pathogenesis of Guillain-Barré syndrome in this patient.

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Photoreception and phonoreception

A comparison of the major afferent pathways in the nervous system

M. Wharton Young, M.D., Ph.D.

PHOTORECEPTION and phonoreception provide the principle means of association between the individual and his external environment. Both vision and audition are made possible through supersensitive teleceptors, for the minute stimuli that activate them arise from remote sources often far removed from the body. In the case of the eye, the light source may be millions of miles away, and, in both instances, the stimulus is transmitted by wave vibrations over the intervening distance.

Physicists have long recognized certain fundamental similarities between light waves and sound waves, and the basic formulas applied to one may be utilized by the other, although certain differences obviously exist. (Light and sound waves may be simultaneously recorded on the same electronic tape for rebroadcasting in color television.) Likewise, there are certain fundamental similarities in the respective parts of the nervous system devoted to the reception of light and sound waves, as well as some obvious differences. It is with these likenesses that we are presently concerned.

Structure is the basis of all function, both normal and pathologic, and no function whatsoever occurs without an associated structural basis. To the anatomist and the scientist, this interdependence is as fundamental an interrelationship as that existing between matter and energy, as expressed in the Einstein equation, $E = MC^2$. Thus, the two greatest teleceptor systems, both designed to receive and react to wave vibrations, are also fundamentally similar, although their likeness is not immediately apparent.

The theory of functional components offers a relatively new concept of the nervous system, since it has been developed in the present century, largely by members of the American School of Neurologists: Strong,[1] Herrick,[2] Johnston,[3] Willard,[4] and others. This concept not only offers a simplification and classification of the nervous system but groups all of the millions of peripheral nerves into only 7 categories based on specific criteria. In such a consideration, the optic and auditory nerves are both included in the special somatic afferent system. (A functional system includes all neurons with certain anatomic and physiologic characteristics in common that enable them to act as a unit.)

The inclusion of the optic and auditory nerves in the same functional system, anatomically and physiologically, led us to seek further similarities within the optic and auditory pathways, and these studies have revealed striking similarities throughout both systems from the outlying peripheral receptors to the cerebral cortex (Fig. 1). The theory of functional components is based largely on phylogenetic and ontogenetic relations rather than on the gross or microscopic considerations. In viewing the developmental aspects of the eye and ear, it becomes apparent that the sensory receptor elements in each organ are of ectodermal origin, even as the entire nervous system is evolved from this outermost layer, which lies adjacent to the environment. In the embryo, the thickened ectodermal placode soon folds to form a closed auditory vesicle, which resembles the optic vesicle in many respects. In these early stages of development, it is obvious that the ectodermal cells forming the walls of both vesicles are the precursors of all the future receptor neurons. The mesodermal tissue that surrounds these early vesicles is destined to form the supporting or connective

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tissues. The vesicular form of these embryonic structures emphasizes the role of the fluid that always constitutes the major part of these receptor organs and further reflects the importance of these liquids in the physiology and pathology of the adult eye and ear.

The specialized receptor cells in the eye and the ear follow a parallel course of development in the embryo. The peripheral outgrowths from the primitive ectodermal rod and cone cells result in an outer nonnuclear layer adjacent to the pigment layer.[5,6] This outer zone of the light-sensitive cell contains the rhodopsin, which is the true chemical receptor substance. Likewise, the primitive organ of Corti presents an outgrowth from the dorsal aspect of its ectodermal hair cells which is similar to that of the rods and cones. This cuticular structure is the tectorial membrane, which is nonnucleated and unmistakably continuous with its parent hair cells.[7,8] The separation between the two areas, usually shown in adult preparations, is an artifact, and, by employing special technics, we have been able to retain the original union between the tectorial membrane and the parent hair cells in the organ of Corti.[9–11]

Many competent investigators have recognized the continuity of the tectorial membrane with Corti's organ; hence, this gelatinous, nonnucleated membrane is made up of the outer peripheral segments of the hair cells, and the two zones are normally united with the aid of these hairlike processes. Electron microscopic studies have shown a similar hairlike union between the nucleated and nonnucleated outer segment of the retinal rods.[12] Thus, the rods are morphologically hair cells. Likewise, one might consider the hair cells of Corti's organ, with their outer tectorial segments, as labyrinthine rods not unlike the retinal rods embryologically, histologically, or, indeed, physiologically (Fig 1). Certainly, the connective tissue elements in the floor of the cochlear duct (basilar membrane) could hardly be as sensitive to the minute sound wave stimuli as the delicate nerve cells with their peripheral outgrowths; hence, the Helmholtz[13] theory appears to be untenable and incompatible with our present concept. The tectorial membrane is much broader in the apical turn than in the basal zone and presents a pennant-shaped contour, with the shorter cell segments in the basal turn and the longer ones in the apical area (Fig. 2). It is well established that the high pitches are received in the lower turn of the cochlea, with short tectorial segments, and the low pitches are received in the upper, with longer segments. The differences between the apical and basal zones of the tectorial membrane are by far greater in width than those of the basilar membrane, which is nonnervous in nature and mesodermal in origin.

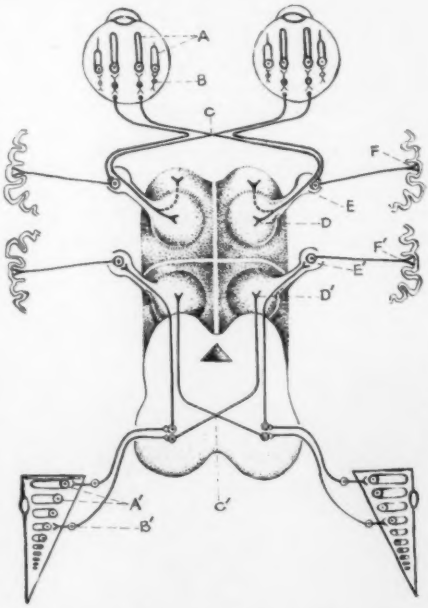

Fig. 1. Diagram showing eye and ear with dorsal view of midbrain. A = rods and cones in retina; A' = hair cells with tectorial membrane attached (rods of the labyrinth); B = bipolar cells of retina; B' = bipolar cells of spiral cochlear ganglion; C = decussation of third neurons in optic chiasm; C' = decussation of third neurons in trapezoid body; D = optic fibers terminating in superior colliculus; D' = auditory fibers (lateral lemniscus) terminating in inferior colliculus; E = lateral geniculate body showing optic relay; E' = medial geniculate body showing auditory relay; F = optic radiations entering cortex (calcarine); F' = auditory radiations entering cortex (temporal). Broken line is optic fiber to pretectal area.

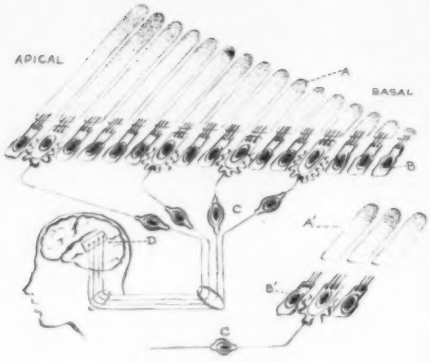

Fig. 2. Diagram showing first two neurons in auditory pathway. Pennant-shaped tectorial membrane is broadest in apical turn. A = outer segment of hair cell forming tectorial membrane; B = inner segment of receptor or hair cell in organ of Corti. A′ and B′ show separation as usually shown between hair cell and tectorial membrane. C = bipolar neurons of spiral ganglion; D = cortical center for hearing.

It is usually the distal end of the primary sensory receptor that presents the lowest threshold to a stimulus and thus constitutes the ultimate nerve "ending." This outermost segment, or ending, is shown most clearly in embryologic development as the peripheral outgrowth from the rods in the developing retina and as a similar dorsal cuticular outgrowth from Corti's hair cells that constitute the tectorial membrane. From the standpoint of morphology, there is very good reason for presuming that sound is received by the distal segments of Corti's hair cells, just as light is received by the outer segments of the retinal rods that contain the rhodopsin.[14]

In phylogeny, also, the outermost zone develops the neuronal characteristics in both the protozoa and metazoa (Fig. 3). Just[15] has emphasized that the outer zone, or ectoplasm, being adjacent to the fluid environment, develops the greatest sensitivity to the environmental changes. As an integral part of the protoplasmic structure, the ectoplasm cannot be divorced from this. The protoplasmic organization, however, much a composite of

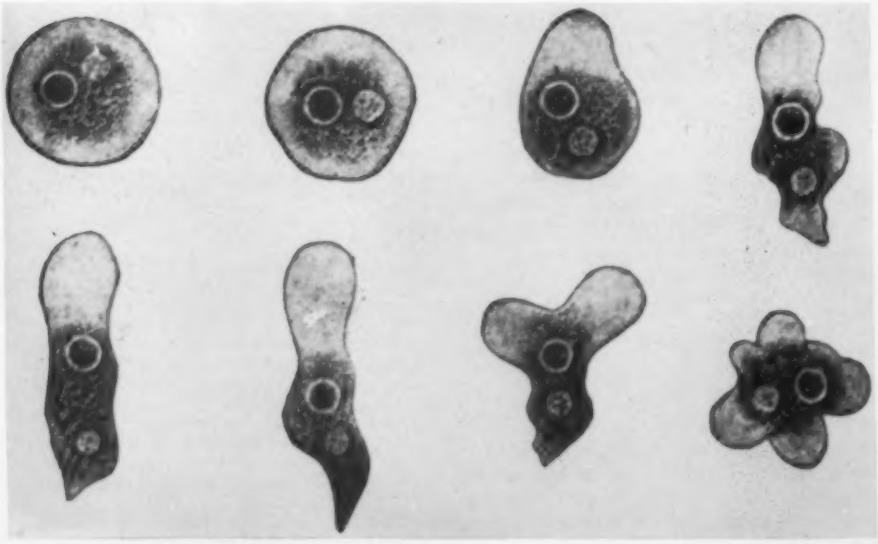

Fig. 3. An amoeba changing from its usual concentric form to a bipolar state by extending its ectoplasm as a pseudopod (after Verworn)

many parts—nucleus with its structures and cytoplasm with its regions—acts as a unit. To conceive of it as such is to approach an understanding of those series of moving events that we call life. The ectoplasm, standing between the protoplasmic system's inner substance and the outside world, reacts first to environmental stimuli and thus conditions the responses of the whole system. Its rapidly occurring, highly active structural changes portray self-regulation and self-differentiation. Thus, by its location and by its peculiar attributes, the ectoplasm becomes the most tangible expression of life processes.[15]

The response mechanisms of the primitive protozoa may reflect the basic structural and functional attributes of adult neurons. When the amoeba wishes to sample the outlying environment before entering it, the ectoplasm is protruded as a pseudopod, or feeler, into the anticipated area (Fig. 3). The cell therefore changes its usual concentric arrangement into a bipolar form that closely resembles the cellular pattern found in both the retinal and labyrinthine rods. There is clearly a proximal nucleated zone of endoplasm and a distal nonnucleated zone of ectoplasm. This structural dualism is closely allied to the "irritability and conductivity" of neurons and is identical to the primary light- and sound-sensitive receptors in adults. Since there are specialized cells that respond to the stimulus of light waves, there must also be comparable specialized cells that respond to the stimulus produced by sound waves. This outer, clear area of the rods contains most of the chemical rhodopsin, upon which light sensitivity depends. One might presume that similar conditions exist in the tectorial membrane—the outer, clear area of the hair cells—and sound-sensitive chemicals are known to exist.[16]

In the primitive metazoa, it is likewise the outer layer or the ectoderm that is strategically located adjacent to the environment, and, hence, the neuronal elements are developed from this layer. The embryonic ectoderm repeats the phylogenetic pattern by giving origin to both the optic and otic vesicles with their highly sensitive receptor cells. This is one reason for classifying the optic and auditory nerves together as a special somatic afferent entity among the functional components. In view of this historic data, one would expect that the derivation of all the light- and sound-sensitive neurons would be solely from the ectoderm, and there is no reason, either in logic or in fact, to presume that the surrounding mesoderm or its derivatives would contribute any sensitive elements to either the ear or eye. The neighboring mesoderm does contribute the supporting and encapsulating tissues of both receptor organs and thus establishes a means of retaining a higher fluid pressure within these organs. These critical fluid pressures greatly influence the ultimate chemicophysical processes upon which functional reception depends, and an increased pressure within the eyeball (glaucoma) or the inner ear (Ménière's disease) may often be the basic cause of blindness or deafness. The logical surgical approach to this problem would be to puncture the outer fibrous coat or retaining wall to permit the escape of the retained fluid and thus reduce its volume and pressure; hence, the established procedure of trephining the eyeball in such cases and likewise fenestrating the ear. It is noteworthy that the surgical opening in both instances is through the outer capsular wall but at some distance from the sensitive receptor membrane. However, the hydraulic results are none the less effective. At the therapeutic level, another basic similarity has been noted: vitamin A has been proved efficacious in certain cases of night blindness, and clinical experience suggests that it may also improve certain selected types of deafness.[17,18]

Stevens[19] has shown that, when decibel units are applied to light and sound, there is a parallel relationship between them from the threshold level up to the maximum intensity for both organs.

SECONDARY AND SUBSEQUENT NEURONS

The basic similarity of the primary receptor neurons that is found in the eye and ear is likewise seen in the secondary and subsequent nerve cells throughout the entire optic and auditory pathways (Fig. 1). The second nerve in each of these afferent paths is bipolar in nature and serves as an internuncial neuron that interconnects the primary peripheral receptor with the third neuron, which reaches the brain stem centers in a bilateral pattern.

In the eye, these bipolar cells form the inner nuclear layer of the retina, the dendrites of which synapse with the rods and cones of the outer nuclear layer, while their axonal processes synapse with the third or ganglion cells in the inner plexiform layer.

In the ear, the secondary bipolar neurons are located in the spiral ganglion, and their dendrites synapse with the primary receptor (hair) cells of Corti's organ, while their longer axonal processes enter the brain stem to synapse with the third neurons of the cochlear nuclei.

The third neurons of both the optic and auditory paths undergo partial decussation and thus have a bilateral distribution at their final terminus in the midbrain and forebrain, wherein each establishes a reflex and a relay connection, respectively (Fig. 1). The specific point-to-point localization of the entire optic pathway has been determined in great detail, and there is evidence that such a pattern is repeated in the auditory path. The tertiary neurons from the nasal half of the retina undergo decussation in the optic chiasm; hence, lesions interrupting the crossing fibers result in bitemporal hemianopsia. No such specific localization is established regarding the tertiary fibers of the auditory path that decussate in the trapezoid body, but some investigators believe they arise mainly from the ventral cochlear nucleus. Both crossed and uncrossed fibers continue forward in the lateral lemniscus to terminate in the inferior colliculus and medial geniculate body. Likewise, crossed and uncrossed fibers course through the optic tract to reach the superior colliculus and lateral geniculate body. The fibers to the respective colliculi establish reflex connections with descending tectobulbar and tectospinal tracts, and, hence, the reflex response to a sudden loud noise may be similar to the response to a sudden flash of light. Phylogenetically, there is an intimate relationship between the optic receptor and superior colliculus and between the cochlea and inferior colliculus. In such animals as the Elasmobranchii and Squalus acanthias, which have well-developed eyes but no cochlea, there is an equally well-developed superior colliculus (optic lobe) forming the entire roof of the midbrain but no inferior colliculus. The latter is developed in higher animals with the development of the cochlea and auditory reflex centers in the caudal part of the tectum.[20]

In spite of their topographic relationship with the midbrain, the geniculate bodies are phylogenetically and functionally a part of the metathalamus, the medial geniculate serving as a relay station for the auditory fibers to the auditory cortex, while the lateral geniculate is a relay station for the optic fibers to the visual cortex (Fig. 1). Precise point-to-point localization has been determined for the retina, lateral geniculate body, and visual cortex. Localization for pitch in the different turns of the cochlea has likewise been determined, and there is considerable evidence that the pattern is maintained in the medial geniculate body and auditory cortex.[21] The geniculate bodies receive some efferent fibers from the cerebral cortex and are connected through brachia with their respective collicular bodies. They each have other diencephalic connections that ascribe to them a more diversified function than mere relay stations to the cortex.

Fibers arising in the lateral geniculate bodies course laterally through the internal capsule to the visual cortex, thus completing the optic pathway.

Fibers arising in the medial geniculate bodies course laterally through the internal capsule to the auditory cortex, thus completing the auditory pathway. Cortical localization has been well established in both the visual and auditory cortex.

Efferent fibers have been described in both the optic and auditory nerves, but their specific function remains speculative.

Vision and hearing are man's most important senses and, hence, are the greatest means of influencing his sensorium and conscious existence.

Blindness and deafness are man's greatest handicaps. Both now occur far too often, and much needs to be learned in these areas if prophylaxis or cure is to be more effective.

SUMMARY AND CONCLUSIONS

The theory of functional components offers a relatively new concept of the nervous system comparable to the periodic table in chemistry; here, the optic and auditory nerves are both placed in the same special somatic afferent

category because of their basic anatomic and physiologic similarities. Further study revealed a distinct parallelism between comparable neurons from the primary sensory receptor cells in the end organs to the corticipetal fibers in the optic and auditory radiations and even to the cortex itself.

Since light and sound are both transmitted to the body from an outside source by wave vibrations, the teleceptors that respond to these stimulating waves would likewise be as comparable as the waves that they receive. Much more is known about the eye and its chemical nature in response to light than about the structure and function of the ear in its response to sound.

Embryologic comparisons show that the retina and tectorial membrane are both of ectodermal origin, that both reveal early vesicular form, and that the ectodermal cells in both cases give rise to bipolar receptor cells of great sensitivity. Like the pseudopod of the amoeba, the outer, or terminal, zone in these primary neurons is a clear, nonnucleated area, the function of which is to respond to a very minute wave vibration. The inner zone is the nucleated area which transmits the initiated nerve impulse to the second, or bipolar, cell in the afferent path. The two adjacent zones in the receptor cell are intimately interconnected by hairlike condensations of the protoplasm in the light- and sound-sensitive cells. The outer zones of the labyrinthine rods constitute the tectorial membrane, which is continuous with the hair cells of Corti's organ. This continuity is well established in the embryo and may be retained, with careful technics, in preparing the adult ear. The alleged separation of the tectorial membrane from its underlying parent, the organ of Corti, is an artifact and must be considered as such.

The light-sensitive rhodopsin is concentrated in the outer, nonnucleated segment of the retinal rods. A sound-sensitive chemical may exist in the gelatinous matrix of the tectorial membrane.

The connective tissue of the basilar membrane, which is mesodermal in origin and nonnervous in nature, could hardly be considered as the sensitive sound receptor that reacts to displacements of 10^{-10} cm., or one one-hundredth of the diameter of a hydrogen molecule. Hence, the century-old concept of Helmholtz is untenable in the light of our present day knowledge.

The second neurons in the optic and auditory paths are distinctly bipolar and are internuncial cells that interconnect the primary and tertiary neurons in both the optic and auditory paths.

The third neurons in both systems undergo partial decussation before reaching their terminus in the midbrain and thalamus, giving each individual ear and eye a bilateral respresentation in all areas beyond their plane of decussation.

Similar reflex connections are established in the superior colliculus for vision and in the inferior colliculus for sound. The reflex reaction to sudden light or sound is somewhat similar, since the descending tectobulbar and tectospinal tracts terminate on the same lower motor neurons of the cerebrospinal nerves.

The fourth neurons, which have cell bodies lying in the medial and lateral geniculate bodies, send their axons through the internal capsule as auditory and optic radiations to reach their specific sensory areas in the cortex as geniculotemporal and geniculocalcarine fibers.

Both the eye and ear are enclosed in a firm, fibrous, mesodermal capsule that maintains a fixed volume and pressure in the dual systems of fluids—vitreous and aqueous humor and endolymph and perilymph—in each peripheral end organ. The surgical penetration of these surrounding walls is used to decompress the eyeball or labyrinth in treating some specific types of blindness and deafness.

The structural or anatomic similarities noted at all levels of the optic and auditory systems are reflected in their functional identities.

The thresholds for seeing and hearing are similar in the decibel scale, as are the other functional levels up to the maximum response for both organs.

The same chemical substance, vitamin A, has been known to improve the function of the eye and ear in selected cases. The pupillary reflex mechanism for light suggests the possibility of a similar reflex mechanism for peripheral adjustments to various intensities of sound. Throughout both of these sensory pathways, there are some motor fibers the

functional significance of which remains speculative.

Further recognition of the basic similarities of photoreception and phonoreception may lead to a fuller understanding of both processes as well as of the chemical nature of nervous function.

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Brain radiation in newborn rats and differential effects of increased age

II. Microscopic observations

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L. R. Bennett, M.D., and R. A. McFall, M.D.

PATHOLOGIC CHANGES develop in the central nervous system of adult animals after irradiation to the head, even though it is generally assumed that the brain is more radioresistant than most other organs. In adult monkeys, astrocytic and neuronal degeneration and changes in the blood-brain barrier were observed after head radiation dosages of 4,500 and 6,000 r,[9] and concomitant neurologic and electroencephalographic abnormalities were observed.[8] In these studies, the brain stem and diencephalon were more radiosensitive than other central areas, a finding supported by the work of Arnold and associates.[10,33,48] Hicks' studies[2,7,49,50] have emphasized the differences in radiosensitivity between fetal and adult brain. Whole body radiation doses as low as 40 r administered to pregnant rats resulted in acute necrosis in the brain, spinal cord, and retina of the developing fetus, but damage to neural elements other than the subependymal cells in the adult rat did not occur unless the animals received 1,200 r or more.

The state of cellular differentiation is usually regarded as a primary factor in determining the relative radiosensitivity of a tissue. Whereas the developing neuroblast is one of the most radiosensitive of cells, the adult neuron is among those most resistant. What are the mechanisms in neuronal maturation, and when do these phenomena occur to change a highly radiosensitive cell into a relatively radioresistant one? Is it firmly established that the effects observed after brain irradiation are primarily due to direct changes within the neuron? To what degree does cerebral circulation altered after irradiation contribute to the neuropathology? These questions are unanswered, and there is less information on effects of irradiation on the brain than most other organs.

The study reported here was undertaken in order to determine the relative radiosensitivity of the rat brain shortly after birth and at varying intervals in the young animal.

METHODS

Newborn rats were irradiated and maintained as described in a previous communication.[51] After varying survival periods, the animals were sacrificed by perfusion-fixation with 10% formalin according to the method of Koenig, Groat, and Windle.[52] The brain of each animal was carefully dissected, further hardened in fixative, embedded in paraffin, and sectioned serially at 10 μ. A variety of staining technics were utilized: thionine, hematoxylin and eosin, Weil's technic for myelin, and connective tissue and blood vessel stains.

RESULTS

General findings. Before discussing the histopathology in detail, a few general findings on the results of this study were of interest. We were interested in observing the eventual production of neurologic signs in the rats exposed to irradiation. A dosage-age graph of our findings is shown in Figure 1. Remember-

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ing that, in these experiments, irradiation was administered to the head alone, it can be seen that significantly lower dosages resulted in the production of neurologic signs (tremors, ataxia, incoordination) if administered during the first postnatal week (to the left of the curve in Figure 1). Animals 7 and 8 days of age required at least 3 times the radiation dose that 1-day-old rats needed to produce the same neurologic signs.

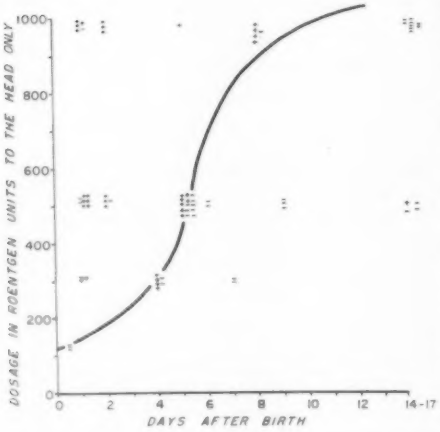

Fig. 1. A graph showing a dose-age curve with respect to the production of neurologic signs by head radiation in the neonatal rat. Most of the animals to the left of the curve had clinical signs involving the nervous system, while most of the animals to the right of the curve did not.

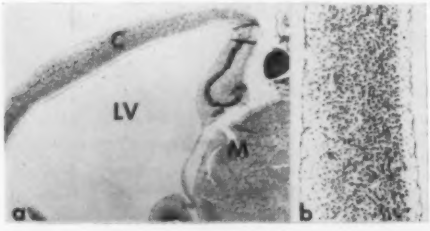

Fig. 2. [A] A transverse section through the midbrain (M), lateral ventricle (LV) and cerebral cortex (C) in a 20-day-old rat that had been given 1,000 r to the head on the second postnatal day. Notice the marked hydrocephalic brain. (× 20) [B] A portion of the cerebral cortex in the animal shown in A, illustrating the closely packed cortical cells. The thickness of the cortex was approximately 50% that of a normal rat at this age. Thionine stain. (× 60)

Microscopic observations. *Choroid plexus.* An inflammatory reaction was observed in the choroid plexus after irradiation. In the more acute studies (forty-eight-hour survival, 500 or 1,000 r), the parenchymal cells appeared swollen and the cytoplasmic material more watery than normal, containing relatively little granular material. At times, focal capillary hemorrhages existed in the choroid plexus, especially that portion of the plexus in the fourth ventricle. In the long-term surviving rats, evidence of these early changes was visible as small contracted scars characterized by connective tissue proliferation.

Ventricular system. Enlargement of the ventricular system was observed in certain rats. In the more severe cases, the lateral ventricles showed a phenomenal dilation as can be seen in Figure 2A, a rat irradiated with 1,000 r on the second day of life and sacrificed after three weeks. In other animals, the cerebral cortex was only slightly displaced by ventricular enlargement. In 1 animal, there was a slight distension of the cerebral aqueduct, but never were marked enlargements observed in the size of the third and fourth ventricles. When the enlargement was in the lateral ventricles, the cortical cells remained very densely packed.

Normal postnatal development of the cerebral cortex is accompanied by an increase in the volume of cortex along with a spacing out of cortical neurons.[39,40] With lateral ventricular distension after radiation, however, the packing density of the cortical neuron looked like that of the 3-day-old rat even though some of these animals had lived from three weeks to three months (Fig. 2). The increase in ventriculer pressure did not appear to destroy the cortical neurons; however, morphologically, the cortical mantle resembled that of a much younger animal.

Meninges. Inflammatory reactions in the meninges were observed in most animals given over 300 r within the first eight postnatal days. Meningitis was usually most intense in animals with the higher radiation dosages. In the acute studies (forty-eight- to seventy-two-hour sur-

vival), the inflammatory reaction in the meninges was characterized by neutrophilic accumulations in the dura and around the vasculature of the pia mater. In this respect, the meningeal involvement is difficult to distinguish from the generalized vasculitis that was often observed. At times, the meningitis was focal in nature, but, with the higher radiation dosages (1,000 r), it was more often diffuse, involving not only the coverings of the cerebral cortex but the meningeal layers under the ventral portion of the midbrain, pons, and medulla (Fig. 3A).

The dura and pial coverings of the brain showed a significant increased thickness in animals of the long-term study. Proliferation of connective tissue (Fig. 3B) and a not too intense secondary mononuclear infiltration was found. These observations were especially seen in animals irradiated between the fifth and fourteenth day with 1,000 r and which survived for nine months to one year. With meningeal thickening, some thickening in the walls of the medium sized and smaller arteries of the pial layer was invariable.

Vascular system. Changes in the vasculature of the brain after radiation in our animals were observed spanning a wide range of pathologic involvement. Certain minor changes were observed, such as endothelial swelling and marked endothelial basophilia (Fig. 4A and B); also observed was focal or widespread perivasculitis (both acute and chronic). Capillary destruction was visible as petechial hemorrhages; long-term thickening of the tunica intima occurred in larger vessels. Occasional necrosis of blood vessel walls was seen, and, in one case, massive cerebral necrosis due to major vascular hemorrhage was noted.

In the short-term studies (forty-eight- to seventy-two-hour survival), the most pronounced vascular phenomena were observed after dosages of at least 500 r in animals radiated within the first five days postnatally and in animals administered 1,000 r before the tenth postnatal day. The most common vascular phenomena observed two to three days after irradiation included endothelial cell swelling, increase in endothelial nuclear basophilia, petechial hemorrhages involving blood vessels at the capillary level, and, in some instances, polymorphonuclear perivasculitis. A

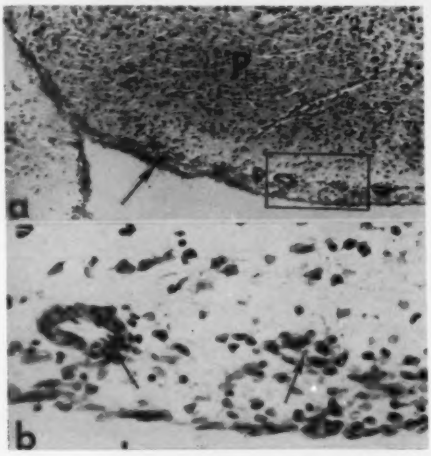

Fig. 3. [A] A photomicrograph showing, in transverse section, the ventral midpontile region in a 23-day-old rat that had been given 1,000 r to the head on the first postnatal day. Notice the thickened meningeal coverings (arrow) and the thickened vascular channels of the pia mater. (× 40) [B] An enlargement of the block outlined in A, showing more clearly the thickened vascular walls (arrows). The lumen of the vessel on the right was almost completely obstructed. Thioine stain. (× 160)

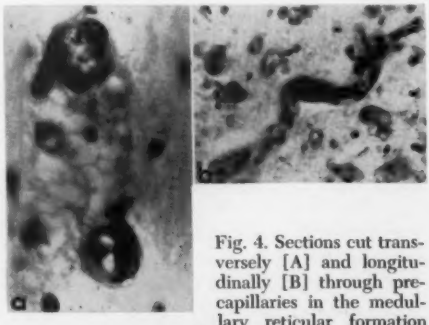

Fig. 4. Sections cut transversely [A] and longitudinally [B] through precapillaries in the medullary reticular formation of a 10-month, 5-day-old rat that had been given 1,000 r to the head on the second day postnatally. Note the thickened vessel wall and increased basophilia. This animal had tremors, a wobbly gait, and other neurologic signs, and most of the small vessels of the brain stem appeared similar to those pictured here. (Thionine stain. A, × 480; B, × 240)

definitive pattern in the vascular pathology of capillaries at this stage seemed discernible. The earliest, most common change with the lowest radiation threshold seemed to be the simple swelling of the endothelial cell cytoplasm with a concomitant increase in nuclear basophilia. As survival time after radiation increased, this process either seemed arrested and reversible (lower dosage of radiation or older rat at time of radiation) or progressed to perivasculitis and capillary rupture presenting a picture of multiple petechial hemorrhage (higher radiation dosage in younger rats).

In the long-term series (survival periods of twenty days to fourteen months), vascular pathology consisted principally of an increase in the thickness of vessel walls with a consequent narrowing of the vascular lumen. This was especially evident in vessels seen within the meningeal layers on the surfaces of the brain (Fig. 3B), although at times deeper vessels also showed unmistakable signs of damage. The thickening in the blood vessel walls was most pronounced in the tunica media and tunica intima, so that the total vessel diameter did not increase but the lumen decreased. Around such fibrosed vessels, signs of a minor chronic inflammatory process often were seen. In these instances, the inflammatory reaction, characterized by mononuclear cells, was possibly the residual of more acute inflammatory reactions observed in the short-term series.

Neurons and neuroglia. Pathologic changes in the brain and brain stem involving neuronal and neuroglial elements were observed after head irradiation during the infant period in our series of rats. Generally speaking, lesions in the nervous system were observed most frequently in animals administered the higher doses during the early postnatal period. No large areas of necrosis were visible in animals sacrificed twenty-four to seventy-two hours after irradiation. In the brains of these animals, however, acute and rather widespread capillary damage was seen, as described above. It seemed as though processes were underway which would result in larger necrotic sites, especially in rats administered 1,000 r, had these animals been allowed to live for longer periods. This assumption seems especially valid since other animals radiated at the same postnatal time and sacrificed one to fourteen months later showed larger lesions in the brain. The areas that were most often involved included the cerebellum, basal ganglia (especially the globus pallidus and caudate nucleus), diencephalon, and medulla (Fig. 5A, B, and C).

In a number of rats, sections of the brain stem showed excessive numbers of neuroglial cells even though no distinct localized lesions could be seen. This "hypergliosis," unassociated with apparent neuronal damage, was most intense in white matter and most frequent in midbrain, pons, and medulla but was also seen in the caudate nucleus and globus pallidus.

DISCUSSION

Studies of Bagg,[3] Job,[4] Wilson,[6] Hicks,[53,54] Warkany and Schraffenberger,[5] and others have established the fact that prenatal developing brain is an extremely radiosensitive organ. Hicks[53] states that "in the rat, starting in the 9th day (prenatal age) irradiation produces severe head and especially brain malformations (anencephaly), anophthalmia on the 10th day, hydrocephalus and other brain deformities on the 11th and 12th days, cord and spinal anomalies on the 11th to 13th days, and various patterns of microcephaly and cerebellar deformities from the 12th day until the neonatal period." In another article, Hicks[54] remarked that "primitive differentiating cells of the nervous system are probably the mammalian cells most easily destroyed by ionizing radiations," and it was found that doses as low as 40 r resulted in cellular necrosis of neuroblasts in less than four hours.

The pathologic findings in the brains of the animals in our series correlated very closely with the neurologic signs described elsewhere.[51] One of the most interesting phenomena was the fact that radiation dosages administered to the brain during the first week postnatally resulted in neurologic signs and neuropathology not encountered when the same dosage was given during the second or third postnatal week. The 15-day-old (postnatal) rat nervous system required at least 4 times the radiation dosage to produce the same neurologic signs and brain neuropathology as the 1- or 2-day-old brain. This quick development of relative radioresistance in the brain comes during a period of very active physi-

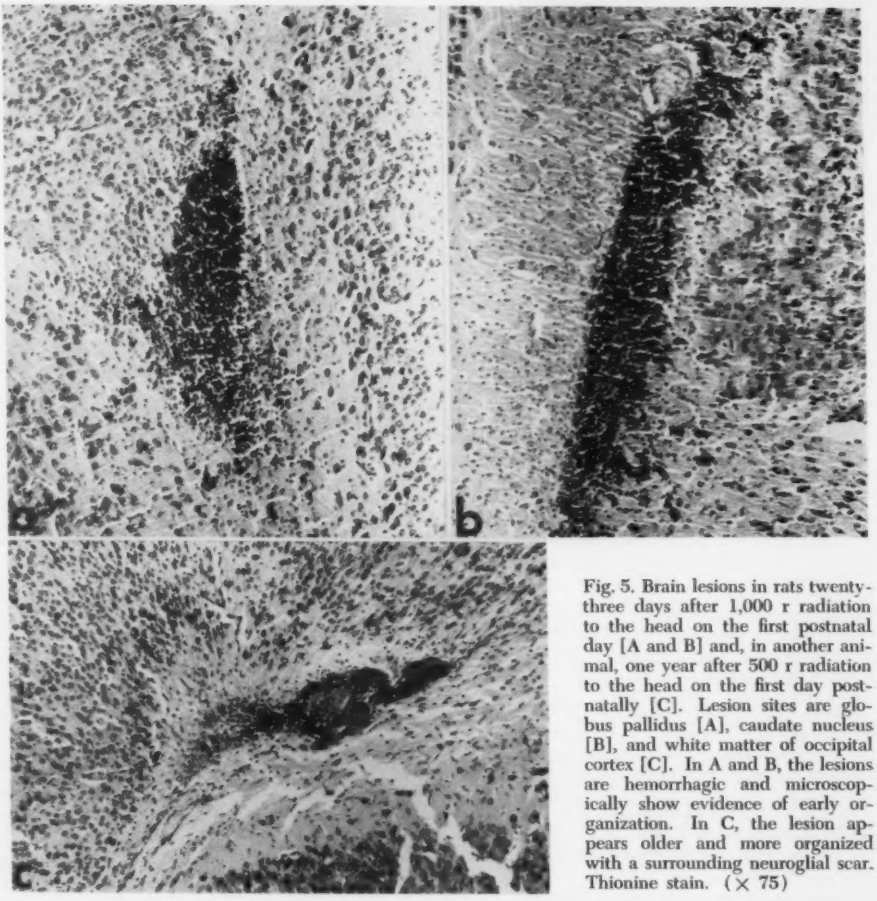

Fig. 5. Brain lesions in rats twenty-three days after 1,000 r radiation to the head on the first postnatal day [A and B] and, in another animal, one year after 500 r radiation to the head on the first day postnatally [C]. Lesion sites are globus pallidus [A], caudate nucleus [B], and white matter of occipital cortex [C]. In A and B, the lesions are hemorrhagic and microscopically show evidence of early organization. In C, the lesion appears older and more organized with a surrounding neuroglial scar. Thionine stain. (× 75)

ologic, morphologic, and biochemical changes in the rat brain. It is during the first two-week period postnatally that the electroencephalogram becomes regular and assumes the characteristics seen in the electroencephalogram of adult rats.[55] During this early postnatal period, the packing density of cortical cells in mouse brain decreases and becomes more like that of the adult. Haddara[39] states that "the packing density of neurons decreases rapidly between the 3rd and 7th day after birth and then more slowly, no change taking place after the 17th day." This would indicate an increase in cytoplasmic constituents along with the development of a more elaborate cortical dendritic system.

These physiologic and morphologic changes in the rat brain during this early period of developing radioresistance are also combined with a dynamic period of biochemical transformation. Thus, oxygen uptake increases steeply, as does the lactic acid production; there are steep rises in the development of actyl- and pseudocholinesterase.[56,57] Water content decreases significantly,[58] and levels of proteins, lipids, and desoxyribonucleic acid rise

markedly. During this early postnatal period, the rat central nervous system appears to be in the same critical state of maturation as fetal guinea pig brain in the last third of its fetal development.[59] The time sequence of our clinical and neuropathologic findings are quite in agreement also with those of Levinson and Zeigler,[60] who found that radiation produced the greatest deficits in learning ability in the rat when the radiation dosages were given during the first four days of life, whereas radiation at the same dosages beyond 18 days of age produced no significant learning decrements.

The cerebellum is perhaps the most incompletely developed portion of the rat brain at birth, and few of the folia visible in the adult are evident at the end of gestation. Notwithstanding this, the Purkinje cells are not thought to divide after the sixteenth day of gestation, although endothelial cell division and cells of the external granular zone probably do continue to divide during the first postnatal week.[61] It would be important to know to what degree neurons or neuroglia in other regions of the brain continue to divide after birth, information that more than likely is forthcoming with studies utilizing radioautographic technics of incorporated tritiated thymidine. From information available at the present time, mitosis in the nervous system is definitely on the decline by birth, but it is difficult to completely rule out the possibility that some of the neurologic and pathologic effects seen in our animals after radiation were the result of radiation effects on cell division. This could not account, however, for the acute and longstanding hemorrhagic lesions. The fact, that often, severe neurologic signs were evident as early as the third postnatal week might also indicate a more widespread direct effect on neurons, neuroglia, and blood vessels. It is our feeling that radiation to the nervous system does not singularly affect one element of the brain such as the neuron, endothelial cell, or neuroglial cell but that each of these elements is radiosensitive to some degree.

The effects of irradiation on the intensive biochemical changes occuring in the rat brain shortly after birth is the area to which we are now directing our attention. In this way, we hope to add some biochemical information to the reasons why a 3-week-old rat brain is relatively radioresistant while a newborn brain is very radiosensitive.

SUMMARY

The heads alone of 112 neonatal rats were radiated with single doses of 125, 300, 500, or 1,000 r. The age of the animals at the time of radiation ranged from 8 hours to 15 days.

A very high degree of correlation was found between the observance of neurologic signs and brain pathology. The brains of animals irradiated during the first three to five days of postnatal life proved more radiosensitive than those of animals irradiated during the latter part of the second postnatal week. This was revealed not only by the onset of neurologic signs but also in the neuropathology.

Pathologic changes were observed in the neurons, neuroglia, blood vessels, and choroid plexus. Hydrocephalus and microcephaly were also noted. Lesions were most frequently found in subcortical white matter, basal ganglia, cerebellum, hypothalamus, and medulla.

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The Centenary of the National Hospital, Queen Square

Russell N. DeJong, M.D.

THE CENTENARY of the National Hospital, Queen Square, was observed during the week June 20 through 25, 1960. It is fitting that we in American neurology, who owe so much of our heritage to British neurology and to Queen Square, should acknowledge this anniversary and congratulate our brothers across the sea.

Neurology was still in its infancy when the National Hospital, the first medical institution established for the care and cure of patients with diseases of the nervous system, opened its doors in 1860. Apart from institutions for the care of the insane and for lepers and those suffering from a few other maladies, hospitals reserved for the treatment of specific diseases were rare until the turn of the century. Duchenne obtained his clinical material by visiting all the general hospitals to which he could obtain admission and by investigating patients in their own homes. Romberg had no wards reserved for neurologic cases. It was some years later that Charcot found his material in the Salpêtrière of Paris, both an asylum and a hospital where large numbers of patients suffering from epilepsy and other chronic nervous disorders were housed. He was able to observe the course of each illness over long periods, often to the postmortem table, and to obtain properly investigated material for the laboratory he established—something that was already in effect in London, at Queen Square.

The lack of facilities to care for victims of chronic neurologic disease in the middle of the nineteenth century was brought to the attention of a small group of philanthropic humanitarians, including two sisters, Johanna and Louisa Chandler, and their brother Edward, whose interest in nervous diseases was aroused by the long illness and paralysis of their grandmother. Funds were raised, partly through the interest of the then Lord Mayor of London, who also had a paralytic affliction. A Board of Management was established, at the first meeting of which the name "The National Hospital for the Relief and Cure of the Paralysed and Epileptic" was established. A lease was obtained on a house at No. 24, Queen Square, Bloomsbury, and in the spring of 1860 the first patients were admitted to the hospital, in which there were 8 beds, consulting rooms, and a dispensary. A need for expansion was ever present, adjoining houses were incorporated (Fig. 1), and during the twenty years between 1865 and 1885 the hospital gradually grew from an ill-adapted old house with meager accommodations to what was at that time a well-appointed building housing about 160 patients. There was continual growth, but no further noteworthy extension occurred until 1934 when the wards and laboratories to the south of the hospital, financed in part by the Rockefeller Foundation, were opened (Fig. 2). Future expansion will provide additional facilities for patient care and research.

Throughout the years, the National Hospital has been not only a haven for the cure of the sick but also a medical school and research center. Teaching in the outpatient department has been a prominent feature from the very beginning. In 1948, when the hospital came under the control of the Ministry of Health, the medical school became the "Institute of Neurology," and two years later it was made a member of the British Post-graduate Medical Federation and a unit of the University of London. Shortly thereafter, the medical school of the Maida Vale Hospital for Nervous Diseases was incorporated with it.

Although it is true that "Queen Square" and "National Hospital" are to Americans synonymous with British Neurology, it is the men who have worked there who come to mind

when we think of the hospital—those individuals whe have personally extended the bounds of neurologic thought and investigation througout the years. It is not possible, in a short article, to do justice to these men, or even to name them all, but some mention must be made of a few of them, for it is they who are, to most neurologists, the National Hospital.

The first physician appointed to the hospital was Dr. Jabez S. Ramskill (1825-1897). While his name is not associated with any notable advance in medicine, he is said to have been an excellent lecturer, deeply interested in the drug treatment of epilepsy. Associated with the hospital from its beginnings to his death in 1897, he must deserve much credit for its development. The second physician appointed was Dr. Charles Edouard Brown-Séquard (1817-1894), the peripatetic neurologist and investigator, who served only until 1863. Although known for his clinical work and investigations, his time in London was devoted mainly to private practice and lecturing, with little in the field of research. At various times

Fig. 1. The National Hospital, Queen Square, in 1866

Fig. 2. The National Hospital, Queen Square, in 1938

Fig. 3. John Hughlings Jackson

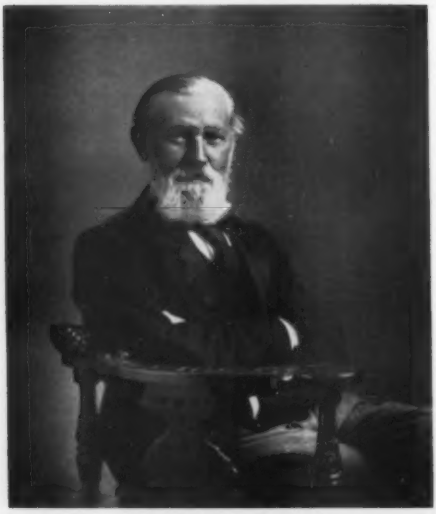

Fig. 4. Sir William Richard Gowers

he worked and taught in Paris, Philadelphia, New York, and Boston. On the death of Claude Bernard, he was elected, at the age of 61, to the Chair of Medicine in the Collège de France, a post he occupied until his death sixteen years later.

The two men whose names stand out most prominently during the early years of the National Hospital are Hughlings Jackson and Sir William Gowers. Very different in their personalities and achievements, they were complementary, and each held the other in high esteem. They both had the ability to observe closely and accurately symptoms and signs of nervous disease.

John Hughlings Jackson (1835-1911) was first appointed an assistant physician to the hospital in 1862 (Fig. 3). His numerous and detailed contributions to neurologic thought, especially those dealing with epilepsy and disorders of the functions of speech, were based on scrupulous clinical observations and minute recording of them. He is best known for his studies on "convulsions beginning unilaterally," although we are also indebted to him for many other contributions to neurologic thought. He was one of the joint editors of *Brain* upon its establishment in 1878. Most of his numerous articles, some published in obscure journals, were collected and edited by James Taylor and published, with a complete bibliography, in two volumes in 1931, under the title *Selected Writings of John Hughlings Jackson*. This has recently been reprinted.

William Richard Gowers (1845-1915) was appointed the first medical registrar to the National Hospital in 1870 and assistant physician two years later (Fig. 4). Although he also made noteworthy contributions to neurology, especially by his investigations on epilepsy and allied states, he was best known for his clinical skill, remarkable insight into the nature of disease, and clear exposition in teaching. His *Manual of Diseases of the Nervous System*, published in two volumes in 1886 and 1888, remained for many years the most popular textbook and reference work on affections of the nervous system in England as well as abroad and was translated into many languages. It has been termed the "Bible of Neurology," and there is still an axiom at Queen Square that no one who imagines he has stumbled upon something novel or obscure should neglect to consult the Manual before claiming originality or hurrying into print.

Other distinguished physicians on the staff

of the National Hospital during its early and later years include, among others, the following: Charles Bland Radcliffe, who succeeded Brown-Séquard; Sir John Russell Reynolds, whose *Diagnosis of Diseases of the Brain, Spinal Cord and Nerves*, published in 1855, was one of the first systematic treatises on nervous disorders in English; Sir Edward Henry Sieveking, who translated Romberg's *Textbook of Nervous Diseases* into English; Thomas Buzzard, a sound practical physician and excellent teacher; Henry Charlton Bastian, best known for his books *Aphasia and Other Speech Defects* and *Brain as an Organ of the Mind;* Sir David Ferrier, one of the pioneers in experimental research on the nervous system and outhor of *Localisation of Cerebral Disease* and *Functions of the Brain;* Howard Henry Tooth, whose name is associated with those of Charcot and Marie from his description of a distal atrophy; Sir Victor Horsley, the father of neurosurgery; James Samuel Risien Russell, one of the most popular teachers in the history of the hospital; Frederick Eustace Batten and James Stansfield Collier, who described, with Risien Russell, the clinical and pathologic features of subacute combined degeneration of the spinal cord; Charles Edward Beevor, who made important observations on the trunk musculature in nervous disease; Samuel Alexander Kinnier Wilson, known for the disease bearing his name as well as his textbook, still in use; R. Marcus Gunn, who demonstrated the value of the ophthalmoscope in providing evidence of systemic disease; Leslie J. Paton, who investigated the pathogenesis of papilledema and optic neuritis; William John Adie, whose pupillary syndrome is well known; George Riddoch, who made valuable contributions to the study of injuries of the spinal cord; the late Joseph Godwin Greenfield, some of whose important contributions to neuropathology appeared posthumously. The above are only some of the outstanding staff members who are no longer living. The distinguished physicians of the staff of the National Hospital who are still living, although some have retired from active work, are known to all who deal with neurology, and to name them would be superfluous. They are the ones who are carrying on the tradition of Queen Square, established so admirably by their predecessors.

American Neurology, and neurologists all over the world, join in congratulating the National Hospital on its centenary. May this one hundred years be but a milestone in the development of neurology throughout the world.

I wish to thank Dr. Macdonald Critchley, who assisted me in the preparation of this article by providing illustrations and allowing me to review, in advance, the page proof of the centenary volume *Queen Square and the National Hospital*, as well as a typescript of his article "The Beginnings of the National Hospital Queen Square," prepared for publication in the *British Medical Journal* at the time of the centennial. Also used as a valuable reference was *The National Hospital Queen Square*, written by Dr. Gordon Holmes in 1953.

Neurologic status of 3-year-old children originally studied at birth

Don Thurston, M.D., Frances K. Graham, Ph.D., Claire B. Ernhart, Ph.D., Peter L. Eichman, M.D., and Marguerite Craft, M.A.

INTEREST in the broad problem of the relationship of possibly injurious perinatal experiences and later developmental defects has always been considerable. While no one doubts that many of these experiences can result in death to the fetus or neonate, opinion has been divided on whether there are residual effects if the organism survives. Gesell[1] repeatedly stressed his belief that a wide variety of defects, neurologic and behavioral, might be traced to brain injury occurring during this period of life and was particularly concerned with the effects of possible "minimal brain damage." He felt that such damage was far more frequent than was usually realized and that its consequences would explain many anomalous defects, including such phenomena as behavior problems, difficulties in learning to read, and so on. More recently, this opinion has been bolstered by the series of studies of Pasamanick, Lilienfeld, Knobloch, and Rogers.[2-6] Investigation of the perinatal history in various impaired groups, ranging from cerebral palsy and epilepsy to behavior and speech problems, has led them to postulate a "continuum of reproductive casualty" which expresses in condensed form the idea that a variety of injurious experiences associated with reproduction may result in a variety of consequences ranging from increased mortality through disabling neurologic damage to the minor behavioral deviations.

The present study was designed to investigate certain aspects of this general problem. In contrast to obtaining retrospectively the newborn history of children with known defects, we have begun with a sample of newborns and have studied their development when they reached the age of 3 years. As newborns, these children were classified into 3 main groups: those whose prenatal and birth experience appeared to be entirely normal, those in whom there was reason to suspect a period of fetal anoxia or who experienced apnea postnatally, and a group with a variety of other complications including prematurity, blood incompatibilities, and frank birth injury. Although 340 children have been reexamined at 3 years, the size of the sample is still too small to attempt to isolate specific injurious factors, as toxemia or placental hemorrhage, within the broad categories. This would necessitate a large scale statistical study of the type now being undertaken collaboratively by a number of institutions under the auspices of the National Institute of Neurological Diseases and Blindness and the National Institute of Mental Health.[7] We are concerned, in this report, with the problem of whether children within the 2 broad groups of perinatal difficulties would later show impairment of neurologic functions as compared with the normal group. The question of impairment in other areas of functioning will be considered in later reports as well as the problem of identifying the individual child who will show subsequent defective development.

Several large, relatively well-controlled studies have been reported in recent years which failed to find any significant difference between normal and perinatally complicated groups.[8-12] Since these results conflict with the conclusions of Gesell,[1] of Pasamanick, Lilien-

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feld, Knobloch, and Rogers,[2-6] and of a number of other human and animal studies,[13-27] possible explanations of these discrepant conclusions were discussed in a previously published article.[28]

One difficulty with a number of studies has been the failure to exclude from control groups children with possible fetal anoxia, congenital maldevelopment, or other injurious factors such as blood incompatibilities. Another problem concerned the broad question of sensitivity in research design. If only gross neurologic defects are to be studied, the frequency of positive findings is likely to be low and will not appear statistically significant unless a very large study is conducted. Alternative solutions are to establish degrees of probable injury — separating those with mild complications from the more severe — or to measure minor as well as major defects. Not only would minor defects be expected with a greater absolute frequency but, by measuring them, information is obtained on a question of importance, that is, whether such minor defects are associated with these complications and may therefore be consequences of the postulated "minimal brain damage."

An attempt was made in the present study to cope with these difficulties. In addition to a strict definition of normality, newborns were evaluated by measures of the blood oxygenation,[29, 30] their behavioral response to test procedures,[31, 32] and weighting significant factors in the over-all medical history of pregnancy, delivery, and neonatal period.[33] In measuring development at 3 years, attention was focused on measuring personality and intellectual and neurologic functions of the sort thought to be especially sensitive to impairment after injury to the brain. The present report concerns only the results of the neurologic examination and only the classification in terms of the over-all perinatal history.

SUBJECTS

All subjects selected for follow-up were born on the inpatient service of a private teaching hospital. Although the subjects of the study are representative within strata and groups of the hospital population, the hospital population itself cannot be considered representative of the general United States population. The socioeconomic level of patients and the quality of prenatal and postnatal care are above average. In selecting subjects for study, 3 methods were employed. First, newborns with postnatal apnea and with other complications, except normal prematurity, exhausted the population of such infants born in the hospital during the period of study. Subjects with signs of fetal anoxia (and without postnatal apnea) were part of a second, essentially unselected sample, and their presence in the study depended only on their being born at the time one of the investigators was on duty on the delivery floor, hence usually in the daytime. Normal full-term and premature newborns were also obtained from the unselected sample, but the total number of such cases was increased by a third selection method, random sampling within sex-race-socioeconomic strata to provide matching with the complicated groups. Subjects obtained by these means who had congenital malformations or other mild or questionable complications were not included in the 3-year follow-up.

The selected cases number 191 normal newborns, 132 "anoxic" newborns, and 98 with "other complications." Normal subjects were infants above 2,500 gm. birth weight, with an uneventful prenatal and neonatal course, who were products of a single spontaneous or low-forceps delivery. Anoxic subjects were those with a period of suspended respiration postnatally or with complications during pregnancy and labor of the sort likely to be associated with reduction of the fetal oxygen supply or signs of fetal distress, as slowing of the fetal heart rate. The exact signs used and a method of weighting them have been previously described.[33] All anoxic newborns were full term, and there was no evidence of any other kind of complication. The group with "other complications" included prematures, blood incompatibilities, frank birth injury, and a few miscellaneous conditions such as hypoglycemia. Birth injury was diagnosed when there was skull fracture, brachial plexus injury, or suspected intracranial injury. More than half of these children also had signs of fetal anoxia or postnatal apnea.

Of the 421 cases selected for follow-up, we were able to examine 355 at 3 years of age, of whom 340 also completed the neurologic ex-

TABLE 1

CLASSIFICATION OF NEUROLOGIC FINDINGS

Normal: No findings present

Essentially normal: One or more of the following deviations

1. Unusual psychologic responses
   a. Observed during examination, as excessive fear, negativism, distractability
   b. Night terrors reported by the mother
2. Breath holding and febrile convulsions reported
3. Speech disturbance
4. Asymmetry of cranium
5. Heterophorias or heterotropias
6. Facial asymmetry
7. Nonspecific gait disturbance, as toeing in, foot eversions
8. Hyperextensible joints
9. Hyperreflexia
10. Hypotonia

Suggestive: Any one of the following, whether or not accompanied by the above "essentially normal" deviations

1. Asymmetric hypotonia of one side or one extremity	11 cases
2. Asymmetric hyperreflexia	4 cases
3. Suggestive facial weakness	11 cases
4. Suggestive facial weakness and asymmetric hypotonia	1 case
5. Neurologic gait	2 cases
6. Ankle clonus	2 cases
7. Suggestive cog wheeling	1 case
8. Microcephaly	1 case

Positive: Any one of the following, whether or not accompanied by the above "essentially normal" deviations

1. One-sided hyperreflexia and one-sided hypotonicity	5 cases
2. One-sided hyperreflexia and probable hydrocephaly	1 case
3. One-sided hyperreflexia and one-sided ankle clonus	1 case
4. Suggestive left facial weakness, left genu recurvatum with hypotonia quadriceps, hyperactive left ankle jerk, left gastrocnemius tightness, suggestive weakness left spinal accessory nerve	1 case
5. One-sided hypotonia and facial weakness	1 case
6. Hemiplegia or hemiparesis	4 cases
7. Definite facial weakness	3 cases
8. Grand mal convulsions with focal features	1 case
9. Right facial hemiatrophy, slight left spasticity	1 case
10. Spastic quadriplegia	1 case
11. Microcephaly with gait disturbance	1 case

amination. The 66 cases, or 15.7% of the sample, lost to follow-up were distributed with chance frequency among the 3 groups of subjects. The major cause of loss was the family's moving out of the geographic range of the study. This accounted for 50 of the 66 subjects; 7 subjects had died (2 of whom were in the normal group) and 3 subjects had to be excluded because of intervening central nervous system trauma. In 4 cases, cooperation with the study could not be obtained, and 2 children had been adopted through agencies that would not allow contact with the adoptive parents.

PROCEDURE

The 3-year examination was a single two to three hour session consisting of psychologic tests followed by a brief neurologic examination. All examinations were conducted without knowledge of the newborn classification, and questions concerning this period were omitted from the history-taking. The neurologic examination was made by the senior author, the pediatrician in charge of the neurologic services of the St. Louis Children's Hospital of the Washington University School of Medicine. In a few instances, children had to be examined by the resident assigned to the pediatric neurology service. These results were reviewed with the regular examiner, and, in several instances where questions were involved, the child was reexamined. The purpose of reexamination was not to provide more extensive examination of questionable cases but to insure uniformity in the method of examination. It was felt desirable that all subjects should be given exactly the same procedure, and the usual clinical practice of carrying out more extensive testing when suspicion of defect arose was not followed.

The neurologic examination included a brief, standard study of the cranial nerves, reflexes, muscle tone, gait, and postural performance as well as observation of general reactions, speech, facies, and so on. Height, weight, and head and chest circumferences were also obtained. Neurologic notes were recorded on a standard data sheet in the form of check marks and descriptive observations. In some cases, a neurologic diagnosis was made, but, except where such a diagnostic label was attached at the time of examination, results are reported in terms of the descriptive observations.

Results of the neurologic examination were classified by a second author, assistant professor of neurology of the University of Wisconsin School of Medicine. As shown in Table 1, 4 categories were distinguished. The classification "normal" includes only children for whom

TABLE 2

PERCENTAGE DISTRIBUTION OF NEUROLOGIC FINDINGS IN 3-YEAR-OLD CHILDREN WITH NORMAL, ANOXIC, OR OTHER-COMPLICATED PERINATAL HISTORIES

Neurologic findings	*Newborn classification*		
	Normal N=153	*Anoxic* N=109	*Other complications* N=78
Normal	47.7	34.9	38.5
Essentially normal	45.1	44.0	37.2
Suggestive	5.2	10.1	17.9
Positive	2.0	11.0	6.4
	100.0%	100.0%	100.0%

χ^2 Normal vs Anoxic 13.66, $P<.01$
χ^2 Normal vs Other 13.46, $P<.01$
χ^2 Among groups 21.09, $P<.01$

there were no recorded deviations of any kind. The second classification is called "essentially normal" and includes deviations that would not usually be a cause for concern and that may not have any significance insofar as central nervous system functioning is concerned. In the absence of other accompanying dysfunction, many physicians would consider these as deviations falling at the extremes of the normal range. On the other hand, most have been implicated as possible indicators of minimal central nervous system injury. One of the purposes of the present research was to determine whether such deviations occur with increased frequency among children with definite neurologic signs and whether they occur with differential frequency in children with differing exposure to trauma. The third classification is "suggestive findings." The evidence of abnormality is not compelling in these cases but does raise suspicion that some kind of central nervous system damage is present. Uncertainty arises because either a finding is not considered sufficient by itself to implicate definitely the central nervous system or the examiner felt the observation to be somewhat questionable. The fourth category, "positive findings," includes children who presented definite neurologic signs indicative of damage to the central nervous system. In addition to listing the findings considered essentially normal, suggestive, or positive, Table 1 records the frequency of cases with each suggestive or positive finding. An individual child is represented only once. If he had more than one of the signs considered suggestive or positive, these combinations are included separately. Many cases classified as suggestive or positive also presented minor deviations which, when occurring alone, were classified as essentially normal. These are not listed in Table 1 but will be presented in Table 5.

RESULTS

The percentage frequency of normal, essentially normal, suggestive, and positive neurologic findings is shown in Table 2 for the 3-year-old groups whose perinatal histories were considered normal, anoxic, or as having other complications. These 3 groups differ significantly from one another, and each of the perinatally abnormal groups shows significantly more defects than the group whose perinatal history was normal. The statistical significance was tested by chi square, as shown in the table, and the probability is less than 1% that such a difference could arise by chance.

In a variety of studies, defects have appeared more frequently with lower socioeconomic status and have also been more frequent in males than in females. In the present study, the 3 main groups had approximately the same proportions of white private, white clinic, and Negro children, so that socioeconomic status differences probably could not account for the difference in neurologic findings. There was a difference in the sex ratio, however. Only 47% of the normal newborns were males, while 60.6 and 56.4% of the anoxic

TABLE 3

PER CENT OF MALES AND OF FEMALES WITH SUGGESTIVE OR POSITIVE NEUROLOGIC FINDINGS AT AGE 3

	Newborn classification		
	Normal	*Anoxic*	*Other*
Males	5.6	22.7	34.1
Females	8.6	18.6	11.8

and other-complicated groups, respectively, were males. If maleness is associated with the presence of neurologic signs, the greater frequency of neurologic findings in the complicated groups might be due only to the fact that they have proportionately more males. Table 3 shows that the results cannot be accounted for in this way, since, in the absence of complicating factors, maleness was not associated with neurologic findings. Males in the normal group actually had a slightly smaller percentage of suggestive or positive neurologic findings than did females. It is possible, however, that sex, while not accounting for the greater frequency of neurologic findings in complicated groups, interacts with complications. The percentage of neurologic findings increased in the complicated groups for both males and females, but the increase was relatively greater in the males than in the females, suggesting that males may be more affected by a complication.

Table 4 shows subdivision of the 3 main newborn groups. By combining the suggestive and positive classifications, it is possible to make some statistical comparisons of the relative frequency of neurologic findings in these various subgroups.

The anoxic group has been subdivided into those with only signs of fetal anoxia, those with a period of postnatal anoxia, and those who were exposed to both postnatal apnea and to probable fetal anoxia. The 2 subgroups with postnatal apnea show a significantly higher frequency of suggestive and positive neurologic findings than the normal groups ($\chi^2=11.54$ and 7.99, $P < .01$ in a one-tailed test), while those with fetal signs alone do not.

The remaining subgroups shown in Table 4 are composed of subjects who were classified in the other complications group. These include prematures with and without signs of anoxia, blood incompatibilities with and without signs of anoxia, and birth injuries. Of these groups, 3 have a significantly higher percentage of neurologic findings than the normal full-term subjects (using one-tailed tests, for anoxic prematures, $\chi^2=3.18$, $P<.05$; for blood incompatibilities, $\chi^2=4.20$, $P<.05$; for birth injuries, $\chi^2=14.11$, $P<.01$). The size of the groups is too small to permit any further breakdown of the anoxic classification into fetal anoxia and postnatal apnea.

Neither the anoxic prematures nor the anoxic blood incompatibilities differ significantly from prematures and blood incompatibilities without anoxia, although the anoxic premature group does show the greater frequency of neurologic findings. It should be noted that the groups were not equated for

TABLE 4

PER CENT OF VARIOUS NEWBORN GROUPS WITH SUGGESTIVE OR POSITIVE NEUROLOGIC FINDINGS AT AGE 3
(The total number of cases in each group is inserted parenthetically)

	No signs of perinatal anoxia		*Signs of anoxia*	
Full-term newborns	7.2	(N=153)	21.1	(N=109)
			Fetal 8.8	(N=34)
			Postnatal 28.3**	(N=39)
			Both 25.0**	(N=36)
Premature newborns	11.8	(N=17)	20.8*	(N=24)
Full term with blood incompatibilities	26.7*	(N=15)	25.0	(N=12)
Birth injury	———	———	57.1**	(N=7)

*P<.05
**P<.01 in a one-tailed x^2 test

TABLE 5

PER CENT FREQUENCY OF VARIOUS "ESSENTIALLY NORMAL" FINDINGS IN 3 YEAR OLDS

Essentially normal findings	*Without other neurologic findings and with a perinatal history that was*			*With other neurologic findings*
	Normal N=142	*Anoxic* N=86	*Complicated* N=59	*All groups* N=53
A. Independent*				
1. Unusual psychiatric reactions	11.3	22.1	20.3	30.2
2. Breath holding or febrile convulsions	5.6	3.5	3.4	1.9
3. Speech disturbance	1.4	0.0	3.3	3.8
4. Asymmetry of cranium	2.1	1.2	0.0	0.0
5. Heterophorias or heterotropias	34.5	24.4	26.2	32.1
B. Not independent**				
6. Facial asymmetry	0.0	1.2	3.3	0.0
7. Gait disturbance	4.2	8.1	4.9	9.4
8. Hyperextensible joints	0.7	4.7	3.3	1.9
9. Hyperreflexia	2.1	4.7	3.3	7.6
10. Hypotonia	7.8	12.8	6.6	7.6

* Findings that may be observed in addition to definite neurologic signs
** Findings that would not be obtained if a more definite neurologic sign were present

sex, degree of prematurity, or severity of the blood incompatibility disease. These factors would, of course, have to be taken into account if any positive conclusions were to be drawn. In the case of the prematures, the mean birth weight of the anoxic prematures was 2,109 gm. and the mean birth weight of the normal prematures was 2,200 gm. This is not a significant mean difference, but it does favor the normal prematures. It would be more difficult to attempt to equate the degree of blood incompatibility disease, and equating has not been attempted. The relatively high frequency of neurologic findings in these children is of particular interest since they were all treated cases. Transfusions were given shortly after birth where it was deemed desirable, or ACTH therapy was employed.

The classification system was described in detail above, and the actual suggestive and positive findings that were obtained were listed. An effort was made to see whether there was any relationship between the type of perinatal complication and the specific neurologic findings, but, with such a small sample, no consistent pattern was observed. It was noted, however, that, of the 8 normal children with suggestive findings, all showed either one-sided hypotonia or suggestive facial weakness. Similarly, of the 3 positive cases with a normal newborn history, 2 presented one-sided hypotonia and one-sided hyperreflexia. The remaining case had hemiparesis.

The deviations listed in the essentially normal classification were those which may or may not have significance insofar as central nervous system functioning is concerned; 2 lines of evidence from the present study may be used to throw some light on the possible significance of these signs. In the first place, if they are related to central nervous system function, such signs would be expected with a relatively greater frequency among children exposed to possibly injurious perinatal factors, especially since it has just been shown that such children do have more suggestive and positive neurologic findings than children with normal perinatal experience. In the second place, if these essentially normal signs are related to central nervous system function, they should occur more frequently among children with other signs of central nervous system injury than among children without such signs.

These comparisons are shown in Table 5.

The essentially normal deviations have been separated into 2 groups: those that can be observed independently of the suggestive or positive signs obtained and those that would not be recorded as essentially normal if a more definite neurologic finding were obtained. Facial asymmetry, for example, would not be recorded in a child who exhibited definite facial weakness, nor could a child showing asymmetric hyperreflexia simultaneously show symmetric hyperreflexia.

Of the 5 signs that can be observed independently of the suggestive and positive findings, only unusual pyschologic reactions occurred with greater frequency among the children with perinatal complications. This greater frequency was statistically significant in comparing the anoxic groups with the normal, $\chi^2=4.03$, $P<.05$. The remaining 5 nonindependent signs tend to occur more frequently in complicated groups, but no differences reach acceptable significance levels.

Similar findings are obtained in comparing the relative frequency of essentially normal deviations in children with and children without signs of central nervous system injury. Unusual psychologic reactions again showed a significant difference. They occurred more frequently in children with neurologic findings (that is, suggestive or positive findings) than in normal children without neurologic findings ($\chi^2=8.74$, $P<.01$). None of the other deviations showed a significant differential frequency.

While, for most of the deviations, the absolute frequencies are too low to provide a very satisfactory statistical test, this is not true of the heterophorias and heterotropias that were present in approximately one third to one-fourth of the children. These were as frequent in normal children without neurologic findings as in either complicated group or children with neurologic findings. As far as the nonindependent signs are concerned, it is difficult to draw conclusions. They tend to occur more frequently in the complicated and suggestive-positive groups. The failure to find a significantly increased frequency could be due simply to the lack of independence.

DISCUSSION

In contrast to the Keith, Norval, and Hunt study[11] and in keeping with results of the Pasamanick and Lilienfeld retrospective studies,[2-6] the present research suggests that neurologic findings are more frequent in 3-year-old children whose birth and prenatal histories are complicated than in normal controls. Possible explanations of this difference in results were discussed above and in an earlier paper.[28]

Children with perinatal complications were divided into 2 main groups: those with signs of anoxia and those with other complications. The anoxic group included children with signs of possible fetal anoxia, postnatal apnea, and postnatal apnea with possible fetal anoxia. Both of the groups with postnatal apnea presented significantly more suggestive and positive neurologic findings than the control group, but those with fetal anoxia did not show an increase that was significant. It may be that these cases of possible fetal anoxia had been exposed only to relatively mild or brief anoxia and consequently would not be expected to show as much of an effect as those in whom suspension of respiration was observed. While it is impossible to equate the degree of anoxia in clinical material of this sort, there is supplementary evidence that does not favor this interpretation. As newborns, the response of the fetal anoxia group to behavioral tests was at least as poor, if not poorer, than that of the postnatal apnea group.[28] Similarly, there appears to be as great an impairment at age 3 in the intellectual functioning of those with possible fetal anoxia. The relationship between the frequency of neurologic residuals and impairment of intellectual functions will be dealt with in greater detail in a subsequent paper. It is sufficient for the present to note that the relatively less frequent neurologic findings in the fetal anoxia group probably cannot be interpreted simply on the basis of a milder complication.

The actual suggestive and positive neurologic findings presented by these children were listed. The majority of the findings would customarily be interpreted in terms of corticospinal or pyramidal tract damage, and the majority of these are asymmetric findings. It is generally thought that hemiplegias are more likely than diplegias to be a result of vascular accidents and, where perinatal complications are involved, to be due to actual birth injury.

However, relatively few of our subjects experienced what would customarily be called birth injury, and the hemiplegias and other asymmetric findings were distributed among all groups of subjects. The conclusion would appear warranted, as Courville[34] has suggested, that perinatal anoxia can lead to injuries similar to those traditionally thought to arise from contusive birth trauma. Courville,[34] Benda,[35] and others have commented that the vascular distribution in the newborn is such as to make the basal ganglia peculiarly susceptible to injury in any circumstances that traumatize the brain.

While the findings commonly associated with extrapyramidal tract and basal ganglia lesions were not frequent in our sample, recent studies have emphasized the difficulty of separating pyramidal and extrapyramidal tract lesions. Both tracts pass through the basal ganglia and are intertwined through most of their course to the surface of the brain. Clinical findings traditionally called pyramidal are known to arise from lesions involving both the pyramidal and extrapyramidal structures.

Some consideration should be given to the nature of the neurologic examination used. This was a screening examination only and did not include the kind of extensive study that would be desirable for full diagnostic evaluation of a patient. Some significant findings will consequently have been missed. This is not a biased procedure, however, and is preferable for research purposes to the practice of examining extensively only those patients who present suspicious findings on initial screening. An opposite tendency may also have been present. Because of our interest in recording all deviations, including minor and essentially normal deviations, it is probable that the total frequency of findings is greater than would be reported in routine practice, where a single isolated sign would receive little attention. This could not, of course, bias the results, since all examinations were made without knowledge of the newborn history and any tendency to overestimate deviations should be distributed equally among the newborn groups. It is probably unnecessary to mention the difficulties involved in a neurologic examination of a 3-year-old child. Extensive experience with such subjects is a prerequisite if any meaningful findings are to be obtained. Since the reliability of observations is necessarily less at this age, the protection afforded by examining without knowledge of the history is of considerable importance.

How consistent the present findings will be over the years is a question about which we can only speculate. It is possible that additional neurologic findings might be presented by these children when they are older. Many of our present observations are fragmentary compared with the typical syndrome in adults. This may be due to either the difficulty of making a reliable examination of a 3 year old or the fact that the typical picture found in the adult has not yet developed. An equally plausible interpretation is that some of the neurologic findings obtained in the present study are more likely to be seen in a young child than at later ages. Many of the postural and motor functions observed as part of a neurologic examination are in the process of developing at this time. While minor lesions might interfere with the acquisition of coordinated functioning and thus be detected during the period of acquisition, with the repeated practice that basic skills of running, walking, and so forth receive, the handicap of the lesion might be overcome and the effects be no longer evident in the practiced performance.

Finally, some comment should be made on the classification of neurologic observations. As previously noted, these were made without knowledge of the newborn history, and the criteria used have been given in detail in Table 1. The deviations considered to be essentially normal were those that might have some relevance for central nervous system functioning, but the question of relevance was debatable. The results of the present research suggest that some of these signs may be more valid than others.

The only sign that was significantly more frequent in complicated groups and in children with neurologic findings than in normal children without neurologic findings was the deviation, unusual psychologic reactions. Although this is not traditionally part of a neurologic examination, an increasing number of neurologists feel that the neurologic examination is fundamentally an examination of behavior and should not be restricted to sensory,

motor, and reflex behavior. This has been emphasized particularly by groups working with children. [36, 37] Present results indicate that the general reactions of children may provide a differential cue to central nervous system injury. A variety of abnormal behavior patterns were summarized under this heading, including excessive fear reactions, withdrawn behavior, generally slow, unresponsive behavior, negativism, flightiness, and rage or tantrum reactions. Reports by the mother of night terrors were also included as perhaps indicating anxiety. A breakdown in terms of the individual patterns has not been attempted in the present report. Since the individual behavior patterns were recorded only when they appeared abnormal, the data are too fragmentary to provide a satisfactory comparison among the kinds of abnormal behavior. A subsequent paper will report similar data in which a number of these characteristics were rated for all children in the sample.

The essentially normal deviation that occurred with greatest frequency was heterophoria and heterotropia. This is an observation that can be made with relatively high reliability, and, while it frequently occurs in the absence of any other neurologic findings and certainly could not be considered a valid sign of central nervous system lesion, it seems quite reasonable to assume that it might reflect very minimal past injury. However, there is nothing in the present study to suggest that this is the case, at least insofar as injury occurring perinatally is concerned. While such a lesion might be more likely to occur as the result of an accident early in fetal life when the eye is developing, this interpretation also appears unlikely since the group of normal newborns showed as great a frequency of heterophorias or heterotropias as either of the complicated groups. While many of the complicated groups were known to have been exposed to unfavorable conditions during pregnancy, none of the normal group had a known history of difficulty although most had been seen by the hospital staff for at least three months prenatally. At present, it seems more likely that this is either a genetically determined pattern or an incompletely developed one. The total frequency of the finding — more than one third of the normal children exhibited it — suggests that it is a temporary imbalance which, in most cases, will be corrected spontaneously with time.

Most of the remaining essentially normal deviations might be described as deviations within normal limits of a characteristic which, when it is pronounced or has a specific pattern, is of significance in indicating central nervous system damage. Thus, breathholding and a tendency to convulse with fever have been thought to reflect a susceptibility to convulsive disorder. Knowledge of this behavior depends upon the mother's report and, in our sample, occurred with low frequency. There was nothing to suggest, however, that it is important as a sign of central nervous system functioning. It occurred more frequently in the normal group. Asymmetries of the cranium and facies are similarly findings, within normal limits, of a pattern which, if it were of a particular type, would be relevant for central nervous system functioning. Again, these findings occurred at infrequent intervals and did not appear differentiating.

Hyperextensible joints, hyperreflexia, and hypotonia are less easily disposed of. Although statistically significant differences were not obtained, they do tend to occur more frequently in the complicated groups or in children with other neurologic findings and this in spite of the earlier discussed factor of nonindependence. The major problem with these signs is determining what constitutes abnormality in a child of this age. For example, when hyperactive reflexes are observed, is the finding comparable to what would be called increased reflexes in an adult or are they only brisk reflexes? With asymmetric findings, one side of the child provides a control for the other, and judgments are always easier and more reliable when they involve comparisons rather than absolute statements. It was partly for this reason and also because the observation "increased reflexes" was never made that symmetric findings were classified as essentially normal while asymmetric findings were classified as suggestive or positive. Had the symmetric findings been given more weight, there would still be differences between normal and complicated groups, of course. However, the inference drawn earlier that the majority of neurologic findings were unilateral should be qualifed by

the recognition that symmetric deviations in tone and reflex activity, if they occurred in the absence of other neurologic findings, may not have been given sufficient weight.

Gait disturbances also present a problem of evaluation. Gait disturbances classified as essentially normal included observations of toeing in, everting the foot, and uneven shoe wear. As with the judgments of tone and reflex function in a child of this age, it is difficult to separate the contribution of immature development from that of central nervous system damage. Perhaps they should not be separated in this case, since the results indicate that such disturbances are more frequent among the complicated cases and are more frequently associated with other neurologic findings.

SUMMARY

A total of 340 children first studied as newborns were reexamined at the age of 3 years. Relationships are reported between perinatal complications and neurologic findings at the time of reexamination. The neurologic examination was made and evaluated without knowledge of the perinatal status.

Suggestive or positive neurologic findings were significantly more frequent in children with a period of postnatal apnea than in normal children or those with possible fetal anoxia. The fetal anoxia group showed a slight increase over the normal group but not a significant one.

Premature children with anoxic signs, children with blood incompatibility disease, and a small group of frank birth injuries also presented significantly more suggestive or positive neurologic findings. Normal prematures without anoxia had more neurologic findings than normal full-term children, but the difference was not statistically significant.

Differences in sex ratio in the groups could not explain the findings, since both females and males showed increased neurologic findings when complications were present. However, the males did appear more susceptible to complications.

The most frequent findings were those commonly interpreted as part of a pyramidal tract syndrome. The majority were asymmetric, but it was pointed out that symmetric changes in tone and reflexes are difficult to evaluate at this age.

A number of supposedly normal deviations that might have significance for central nervous system function were evaluated singly to determine whether they occurred more frequently in the complicated groups and whether they were more frequent among children with neurologic findings.

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Hemorrhage into pituitary adenoma with spontaneous recovery and reossification of the sella turcica

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ACUTE HEMORRHAGE into pituitary tumors is attended by fulminant symptoms and a high mortality rate. Of 36 patients who showed this syndrome in the acute form,[1,2] 22 died either in minutes or within a few hours to a month. Of those who survived, some recovery of vision or ocular movements or both was noted in at least 9. Some authors have related these lesions to the development of Simmonds' disease[3] or severe hypopituitarism[4] that contributed to mortality and morbidity. Operative intervention has resulted in a favorable outcome in several instances. However, spontaneous recovery from bleeding into a presumably eosinophilic adenoma observed by Cairns[5] and in another instance by Jefferson[6] is a rare event.

The case to be reported is another striking example of spontaneous recovery from hemorrhage into a pituitary adenoma, which, in addition, was accompanied by reossification and marked reduction in size of the previously greatly enlarged sella turcica. Reconstruction of the sella turcica after surgical and/or radiation therapy has been previously observed,[4,7] but we were unable to find another report of spontaneous sellar reconstruction in the literature. We, therefore, consider the unique clinical and roentgenologic features of this case worthy of report.

CASE REPORT

A 30-year-old white mechanic was transferred to the Bronx Veterans Administration Hospital on March 5, 1952, after two and a half weeks' hospitalization in St. Elizabeth Hospital, Elizabeth, N. J., with a diagnosis of subarachnoid hemorrhage, pituitary adenoma, and possible intracranial aneurysm.

History. About two weeks before onset of acute symptoms, the patient sustained a slight head injury. While rising from a kneeling position, he struck the middle third of the vault of his head against a flat-angle iron bar. Although stunned, he did not lose consciousness.

On February 16, 1952, at 11 p.m., the patient was awakened from sleep by a splitting headache over the entire skull, followed later by nausea and vomiting. The headache persisted in spite of medication. The following day, the patient had a high fever, became confused and lethargic, and "went out of his mind," later being unable to recall anything that occurred during the next two days. On February 19, he was admitted to St. Elizabeth Hospital with a diagnosis of meningitis. On admission, he appeared confused and lethargic and had stiffness of the neck, a temperature of 105° F., and blood pressure of 90/50 mm. Hg. The next day, the patient was much improved and talked rationally; neck rigidity and Kernig sign had disappeared. In spite of improvement in general status, during the first week, an almost total left internal and external ophthalmoplegia with ptosis as well as temporal hemianopsia gradually developed. Finally, sudden amaurosis of the left eye appeared. The right eye also showed marked impairment of movements as well as sluggish pupillary reaction to

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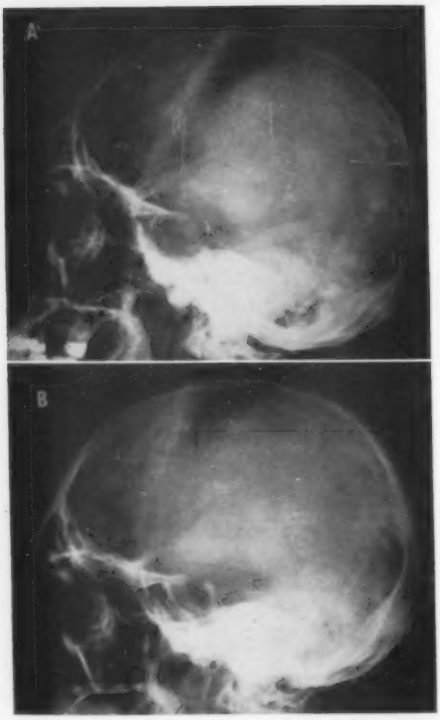

Fig. 1. [A] Roentgenogram of skull (March 7, 1952) shows enlarged sella turcica with erosion of the floor, posterior clinoids, and dorsum sellae. [B] Roentgenogram of skull (May 6, 1958) demonstrates reossification and marked reduction in size of the previously ballooned sella

light and on near vision. The fundi appeared normal on examinations by neurologic and ophthalmologic consultants. Visual field examination on March 3 revealed concentric contraction, more marked in both temporal fields; the movements of the left eye appeared improved in comparison to the first ophthalmologic examination. The vision in the left eye returned gradually, first in the nasal and then in the temporal field. On March 5, the patient was transferred to the Bronx Veterans Administration Hospital in a markedly improved condition with paresis of the right abducens nerve but no subjective complaints except for double vision. The transfer summary revealed additional data. Lumbar puncture on February 21 revealed an initial pressure of 152 mm. H_2O; the 5 cc. of clear spinal fluid removed showed sugar, 69 mg. per cent; protein, 100 mg. per cent; Pandy, trace; and cell count, 4 white blood cells. A second lumbar puncture showed a pressure of 176 mm. H_2O, slightly xanthochromic fluid, 12 cells, 2+ Pandy; and 69 mg. per cent of sugar. A blood culture on February 26 showed no growth. Blood and spinal fluid Wassermann was reported as negative. On February 28, an air encephalogram was carried out and was reported as "normal."

The family history of the patient was not contributory. The patient has been married for eight years and has two healthy children.

The previous history revealed an episode of a "running ear" during 1943 while he was in the armed forces, with a recurrent episode six months ago. The patient had shown normal growth and development and had begun to shave at 15 or 16 years of age but only once a week up to the age of 21 and twice weekly up to the age of 28. He was always robust and heavy and played fullback on his football team. However he stated that, during the year before onset of acute symptoms, he again shaved only once a week, had sexual intercourse only twice a month and drank a great deal of water; he had gained 35 lb. in body weight in the six months before admission.

Examination. The patient was well-developed, athletic-type man without obvious stigmata of endocrine dysfunction; he appeared somewhat pale but was otherwise normal in general physical and mental status except for mild lethargy. The general physical examination did not reveal any abnormalities except for perforation of the left tympanic membrane. Temperature was 98° F., pulse, 70 per minute, and blood pressure, 100/70 mm. Hg. On neurologic examination, the patient showed normal stance but slightly awkward gait with normal arm swing. Motor and sensory functions were intact. Mild hyperreflexia in the left extremities with equivocal Babinski and positive Mendel-Bechterew response on the same side was noted. Cranial nerve study showed smell decreased on the left and, paralysis of the left external rectus muscle with equivocal weakness of the left superior rectus muscle.

Diplopia field studies confirmed only the presence of left abducens paralysis. The visual acuity was 20/25+3 in the right eye and 20/20–3 in the left. Peripheral visual fields revealed partial bitemporal hemianopsia more advanced on the right. Central fields could not be obtained at this time because of imperfect cooperation. The fundi showed normal outline and color of disk, with normal physiologic cup. The function of the cranial nerves was otherwise normal.

Course. Roentgenograms of the skull showed the sella turcica markedly enlarged in all diameters (Fig. 1A) with erosion of the floor, posterior clinoids, and dorsum sellae. Also, the choroidal glomera were calcified. Electroencephalography revealed a mixed but generally slow 6- to 7-per-second background activity with a fair amount of low voltage, fast patterns. On several occasions, a slower frequency range was noted in the left hemisphere, particularly in the motor and posterior temporal area.

Urine was normal and fluid intake and output were within normal range. Complete blood count on several occasions revealed normal values for hemoglobin and red blood cells; the white blood cell count ranged between 3,000 and 4,000 cells, with relative lymphocytosis of 60%. The basal metabolic rate was −17%. In endocrine studies, a twenty-four hour urine specimen taken March 11 revealed 4.2 mg. of 17-ketosteroids. An examination on March 31 showed 17-ketosteroids of 5.5 mg. and 11-oxysteroids of 11.05 mg. in a twenty-four-hour specimen before the administration of 25 mg. of ACTH by intravenous glucose-saline infusion over six hours; the following day, 12 mg. of 17-ketosteroids and 1.48 mg. of 11-oxysteroids were found in the twenty-four-hour specimen. The Thorn test showed a 57% drop (123-54) in eosinophils after 25 mg. of ACTH. Radioisotope studies with iodine on March 28 were consistent with the diagnosis of hypopituitarism. Other laboratory studies revealed the following: CO_2, 53 volume per cent; chlorides, 106 mEq. per liter; Na, 145 mEq. per liter; K, 4.3 mEq. per liter; cholesterol, 163 mg. per 100 cc.; and cholesterol ester, 128 mg. per 100 cc.

A lumbar puncture on March 7 revealed red blood cells, probably due to traumatic puncture, but no xanthochromia. The spinal fluid protein was 102 mg. per cent; a compliment-fixation test was negative, as was the spinal fluid culture.

Fig. 2. Left carotid angiogram demonstrating elevation of anterior third of middle cerebral artery (arrow)

On the basis of clinical and laboratory data, a diagnosis of hemorrhage into a pituitary adenoma was made. In order to exclude the possibility of intracranial aneurysm, left carotid angiography was done and showed an elevation of the anterior third of the middle cerebral complex but no evidence of an aneurysm (Fig. 2).

During the course in the hospital, the patient progressively improved. Repeated peripheral and central visual fields appeared normal, the visual acuity remaining oculus dexter 20/25+3 and oculus sinister 20/20–3. The abducens paralysis had disappeared at discharge on April 25. In view of marked improvement, neither neurosurgical nor radiologic therapy was advised. The patient was followed in the Neurosurgical Clinic at regular intervals up to the time of this writing. He has remained free of clinical symptoms or signs of neurologic or endocrinologic disturbances. Roentgenograms of the skull during 1957, 1958, and 1959 revealed a striking reossification (Fig. 1B) and marked reduction in the size of the previously ballooned sella turcica. A photograph (Fig. 3) shows the appearance of the patient five years after the acute episode.

During a recent examination (May 5, 1959),

Fig. 3. Appearance of patient on March 5, 1957, five years after the acute episode

the patient related that he considers himself entirely normal and free of previous symptoms. Shortly after the discharge in 1952, he began to shave daily up to the present time. Sexual intercourse is now of normal frequency; 2 children were born after 1952. His body weight, which rose from 185 to 220 lb. six months before the illness in 1952, is now again at the normal level. The fluid intake returned to a normal range, his appetite is good, and he sweats normally. He is as active as any other person in his group, and his vision is normal subjectively and objectively. The eye grounds show optic disks with sharp outline and color and normal cup and venous pulsations; the eye movements and reactions of pupils are within normal range.

DISCUSSION

Without pathologic verification, the diagnosis of hemorrhage into a pituitary adenoma remains presumptive, although the evidence in our case strongly supports such a diagnosis. As an explanation for the striking spontaneous recovery, destruction of the pituitary adenoma is postulated with selective preservation of enough normal glandular tissue to maintain normal endocrine function. Most authors agree that the clinical symptoms are rather uniform, consisting of sudden onset of headaches, nausea, and vomiting, stiff neck, drowsiness, confusion or coma, diplopia, ophthalmoplegia, amblyopia, and, rarely, hemiparesis.

Aneurysms of the internal carotid artery of the circle of Willis may at times simulate a hypophyseal tumor with asymmetric or symmetric enlargement of the sella[4,8] as well as primary optic atrophy and hemianopsia,[9] not to speak of their propensity to cause subarachnoid and intracerebral hemorrhage, which in turn may suggest a diagnosis of pituitary apoplexy. Also, signs of pituitary dysfunction have been observed with intracranial aneurysm.[10] Finally, the coexistance of pituitary adenoma and intracranial aneurysm should be kept in mind as a rare possibility.[11,12] For all these reasons, an arteriogram appears to be the most appropriate test to exclude the presence of aneurysm or other abnormalities such as angioma or intracerebral tumor, which may have been the cause of a subarachnoid or intracerebral hemorrhage. On the other hand, the arteriogram may demonstrate the presence of parasellar tumor with findings occasionally resembling those of temporal lobe tumor.[13] It is needless to say that a pneumoencephalogram if at all tolerated by the patient, may contribute to further elucidation of the case.

Concerning the nature of the underlying pathologic process, it is generally accepted that, in most cases, the tumor outgrows its blood supply, which leads to hemorrhage and/or necrosis. These may occur separately or occasionally may coexist in unequal degree.[14] Zülch[15] pointed out that regressive processes, like hydropic swelling going on to liquefaction and cyst formation, are very common in the average chromophobe adenoma, while eosinophilic adenomas, because of hemorrhage within the tumor, often present a brownish color. Müller and Pia[16] described the extreme thinness of blood vessels in pituitary adenomas as a reason for hemorrhage. Acute hemmorrhage occurs, however, in chromophobe and eosinophilic adenoma. Brougham, Heusner, and Adams[14] concluded from their available material of only 12 cases that, considering the greater frequency of chromophobe adenomas (80%), hemorrhage occurs relatively more often in eosinophilic tumors. They found no reports of similar changes in basophilic or verified fetal-cell or transitional-cell adenomas. Furthermore, they stated that there was no definite relationship to malignancy of the adenomas in the observed cases. Müller and Pia,[16] after a review of 58 cases, were not convinced of a relative higher frequency of hemorrhage into eosinophilic tumors.

The importance of a careful assessment of the endocrine status as an essential base line for further diagnosis and therapeutic management as well as in early recognition of panhypopituitarism in vascular lesions of pituitary adenomas has been stressed by several authors.[1,4,14,16] Although extreme insufficiency in chromophobe adenomas is admittedly uncommon,[17] a typical case of Simmonds' disease occurred after sudden hemorrhage had destroyed most of the chromophobe adenoma and the remainder of the anterior lobe.[3]

In the production of the fulminant symptoms, aside from the signs caused by compression of the optic pathways and the contents of the cavernous sinus (the third through sixth nerve and cartoid artery), further suprasellar extension may embarrass the intradural portion of the carotid artery and oculomotor nerve and, finally, the hypothalamus and other parts at the base of the brain.[4,14,16] Blood may escape into the subarachnoid space, although this is less common as compared to bleeding from aneurysms or in intracerebral hemorrhage, or there may be at least an inflammatory reaction within the basilar cisterns.[4] It is the sudden compression of diencephalic structures by expanding tumor or hematoma which is probably responsible for the paralytic effects leading to immediate collapse and death, as observed by Dingley,[18] who reported the case of a man who fell dead after running for a moving bus. On the other hand, secondary mechanisms, such as blockage of cerebrospinal fluid pathways with subsequent hydrocephalus, edema, hemorrhagic infarction, or hematoma of temporal lobe with development of an incisural herniation of the hippocampal gyrus, may lead to a more protracted onset of drowsiness, coma, hyperthermia, and other vegetative disturbances. Acute hypopituitarism with resultant addisonian crisis attended by hypotension and hypoglycemia is another cause for the development of drowsiness, confusion, and coma within a few hours or days in some cases.[14] Occasionally, development of hemiplegia[19] or hemiparesis as well as convulsions[14] due to either compression of major arteries or intracerebral extension of tumor or hemorrhage may render the diagnosis more difficult.

In the majority of cases, hemorrhage occurred spontaneously;[1,16,20] in several instances, it was observed during the course of radiotherapy[1,20,22] and rarely as the result of trauma.[1,16,23] Our patient sustained a mild to moderately severe head injury two weeks before onset of the acute episode; however, the significance of the injury remains doubtful.

From a review of 75 cases reported in the literature,[1-3] it is obvious that spontaneous recovery to symptom-free status, as in our case and those of Cairns[5] and Jefferson,[6] is the exception rather than the rule. In most patients who survive the initial apoplectic insult, the prognosis remains grave in respect to survival, recurrences, and permanent neurologic impairment.[1] If, under general supportive measures, endocrinologic replacement therapy, and, perhaps, judicious preoperative use of hypothermia, the patient reaches a plateau that allows definitive measures, surgical intervention should be given serious and early consideration. Although good results after surgery have been sporadically reported in the past,[21-24] a more hopeful attitude as expressed in recent years[1,4,16,20,25-28] is justified, particularly in the light of advances in endocrine therapy, anesthesia, and surgical technic. Müller and Pia[16] cited 15 instances in which immediate surgical intervention prevented a fatal outcome, and Shenkin[28] reported relief of amblyopia in pituitary apoplexy by prompt surgical intervention.

Since radiation therapy has been accepted as a causative factor in several cases of hemorrhage into a pituitary neoplasm and occasionally as the apparent reason for exacerbation after pituitary apoplexy,[4] continuation or institution of radiotherapy is generally not advisable under these circumstances.

On the other hand, the possibility of rather complete, spontaneous, and lasting recovery should not be lost sight of. As some authors[14,16] have pointed out, treatment should remain conservative as long as the clinical course moves in the direction of recovery.

SUMMARY AND CONCLUSIONS

1. Acute hemorrhage into pituitary tumors is usually a grave event attended by a high rate of mortality and morbidity. Spontaneous recovery has been observed in only a few instances.

2. The case of a 30-year-old mechanic who

recovered spontaneously from the acute episode of bleeding into a presumably chromophobe pituitary adenoma was described. In addition, the patient lost all endocrine symptoms that preceded the apoplectic event. It is assumed that the hemorrhage destroyed the pituitary adenoma but spared enough glandular tissue to maintain normal endocrine function throughout a seven-year period of observation.

3. The clinical improvement was accompanied by reossification and marked reduction in size of the previously greatly enlarged sella turcica. Reconstruction of the sella after surgical and/or radiation therapy has been observed before, but spontaneous sellar reconstruction appears to be a unique observation.

4. A review of the literature revealed 75 cases of hemorrhage into pituitary tumors. Of 36 patients who presented the syndrome in the most acute form, 22 died and recovery remained incomplete in 9. The prognosis also remains guarded, particularly in respect to recurrences and permanent neurologic impairment, in patients who survive an initially less severe or subacute attack.

5. The diagnosis, etiology, pathophysiologic mechanisms, and contributory factors such as trauma or radiation therapy were discussed in the light of available data.

6. In view of the grave prognosis, early surgical intervention is generally recommended. Good results after surgery were reported only rarely in the older literature, but more recent surgical experiences offer a far better outlook. The institution or continuation of radiation therapy is usually inadvisable. On the other hand, the possibility of spontaneous recovery, as in the case reported, may justify adoption of a conservative regimen if warranted by a favorable course in the direction of recovery.

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Some descending vestibular projections in the medulla oblongata and spinal cord

Leo C. Massopust, Jr., Ph.D., with the technical assistance of H. J. Daigle

CONSIDERABLE uncertainty exisits in the literature over the termination of vestibulospinal fibers.[1–13] It is well known that two distinct vestibulospinal systems exist: [1] the medial vestibulospinal tract, which is a component of the descending medial longitudinal fasciculus, and [2] the lateral vestibulospinal tract, occupying the ventrolateral portion of the medullary reticular formation.[12,13] Lateral vestibulospinal fibers arise largely from the lateral vestibular nucleus and course caudad, maintaining an uncrossed ventrolateral position through the medulla oblongata and finally entering the sulcomarginal bundle of the cervical spinal cord along with medial vestibulospinal fibers from the medial longitudinal fasciculus.[1,3,4,6–8]

The extent and termination of the foregoing descending vestibular systems in the spinal cord remains uncertain since most of the previous studies of the vestibulospinal system were accomplished through the use of the Marchi method.[14–16] Because of the difficulties encountered in tracing fine or lightly medullated fibers to their termination by this method,[17] it was decided that a bioelectric investigation of the vestibulospinal systems might be more advantageous. Since most of the uncertainty is concerned with the manner in which the vestibulospinal component of the medial longitudinal fasciculus terminates in the spinal cord, special attention was given to this problem.

MATERIALS AND METHODS

These experiments were performed on 16 cats of both sexes anesthetized with Nembutal. They were brought to a light anesthetic level that preserved their reflexes but prevented voluntary movements.

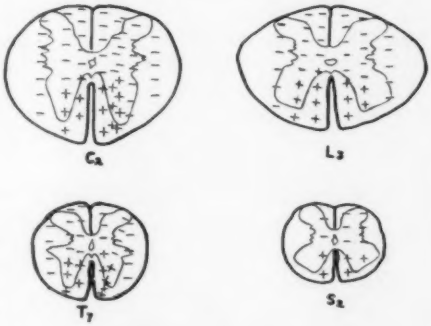

Fig. 1. Composite diagrams of typical sections of the 4 regions of the spinal cord, showing the characteristic map obtained during multpile insertions and withdrawals of recording electrode. Areas yielding characteristic 2-peak or single peak potentials are indicated with (+). All other areas recorded from are indicated with (—).

The occipital plate of the skull was removed, exposing the cerebellum. By means of a suction apparatus, the posterior half of the cerebellum was removed, including most of the nodule and part of the uvula. This procedure exposed the floor of the fourth ventricle. By visualization of certain landmarks on the floor of the fourth ventricle, bipolar concentric silver electrodes measuring 0.3 mm. in diameter were placed unilaterally in the regions occupied by the medial and spinal vestibular nuclei. Insertion of the electrodes was accomplished by means of a Baltimore or Labtronic stereotaxic instrument.

Similar bipolar, silver-coated, concentric

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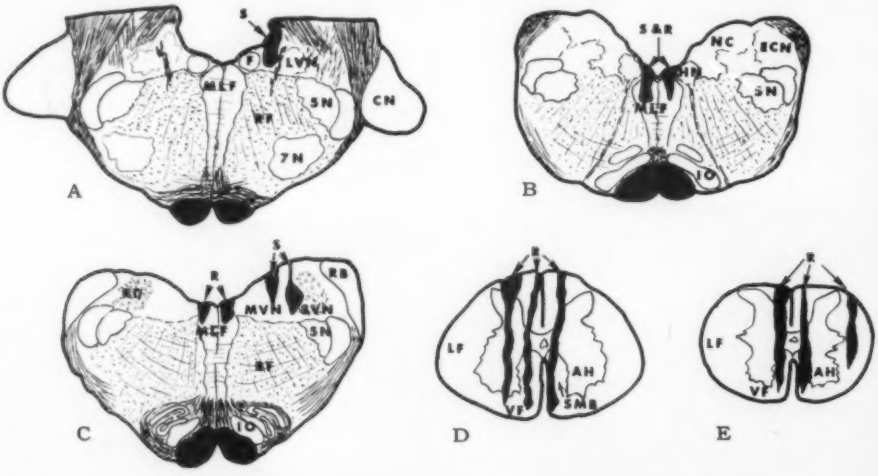
stimulating electrodes were placed visually in various positions along the ipsilateral or contralateral bundles of the descending medial longitudinal fasciculus. Likewise, recording electrodes were placed either ipsilaterally or contralaterally, according to a preestablished insertion pattern (Fig. 1), in various segments throughout the spinal cord. This was accomplished by exposing 1 to 2 cm. of the cord through removal of the spinous processes, then excising the epidural fat and incising the dura mater. Specially designed spinous process clamps adapted to the Labtronic stereotaxic instrument were used to hold the vertebral column rigid adjacent to the exposed parts of the cord while recordings were made from the various segments.

The vestibular nuclei complex or the medial longitudinal fasciculus was stimulated with single threshold (0.3 to 4 volts) rectangular pulses generated by a Grass Model S4B stimulator. These pulses were synchronized with the sweep on a Dumont Type 322A oscilloscope after the usual preamplification through a Grass Model P5R preamplifier. Photographs of the oscillographic sweeps were made with the Grass Model C4D kymograph camera. In all experiments, voltages and currents delivered to the animals were monitored on a specially designed secondary oscillographic system.

On termination of each experiment, the cats were perfused with saline and 10% formalin. The brain and spinal cord segments were



Key

AH	= Anterior gray horn	NC	= Cuneate nucleus
CH	= Cochlear nucleus	R	= Recording electrode site
ECN	= Accessory cuneate nucleus	RB	= Restiform body
F	= Genu of the facial nerve	RD	= Radix of vestibular nerve
HN	= Nucleus of the hypoglossal nerve	RF	= Reticular formation
IO	= Inferior olivary nuclei	S	= Stimulating electrode site
LF	= Lateral funiculus	SMB	= Sulcomarginal bundle
LVN	= Lateral vestibular nucleus	SVN	= Spinal vestibular nucleus
MLF	= Medial longitudinal fasciculus	VF	= Ventral funiculus
MVN	= Medial vestibular nucleus	5N	= Nucleus and tract of the trigeminal nerve
		7N	= Nucleus of the facial nerve

Fig. 2. Tracings of magnified sections of typical stimulating and recording sites in various experimental animals. [A] Most rostral point of stimulation at the level of the cochlear nuclei and genu of facial nerve. [B] Stimulating and recording sites just rostral to the calamus scriptorius in caudal medulla. [C] Stimulating and recording sites at a level of approximately midmedulla. [D] Typical series of insertions of recording electrode at the upper lumbar level of the spinal cord. [E] Typical series of insertions of recording electrodes at the midthoracic level of the spinal cord.

stored in formalin and, after a few days, were sectioned on the freezing microtome and stained with Sudan black B.

RESULTS

Characteristics of vestibular responses in medullary medial longitudinal fasciculus. The stimulating electrodes were placed in the medial or spinal vestibular nucleus at a level just rostral to the facial colliculus (Fig. 2). From the recording electrode, which was placed in the ipsilateral medial longitudinal fasciculus opposite the medial or spinal vestibular nucleus, single negative peak responses were elicited at a threshold of 0.3 to 0.5 volts (monitored). This response had a latency of about 2 msec. and was characterized by a relatively high amplitude, slow wave, negative type of response (Fig. 3). This same type of response was also found when the rostral medial longitudinal fasciculus was stimulated at the level of the facial colliculus and recordings were made in the ipsilateral medial longitudinal fasciculus just rostral to the calamus scriptorius. Occasionally, this slow wave response was seen arising on the descending limb of the stimulus artifact. When this occurred, the potential appeared to spread, taking 4 to 5 msec. to reach base line. Normally, the negative evoked potential was slow in character with a somewhat rounded peak and took 2 to 3 msec. to reach base line. In recordings from the contralateral medial longitudinal fasciculus at the same position mentioned above, the single negative peak response was depressed, although its characteristics remained the same (Fig. 3B).

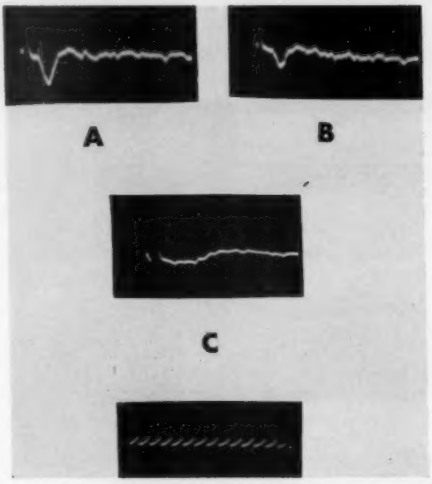


Fig. 3. Typical evoked negative potentials observed by stimulating in either the medial or spinal vestibular nucleus or the rostral medullary medial longitudinal fasciculus and recording in the caudal medullary medial longitudinal fasciculus [A] Potential recorded from the ipsilateral medial longitudinal fasciculus. [B] Potential recorded from the contralateral medial longitudinal fasciculus. [C] Loss of potential after section of the medial longitudinal fasciculus between the recording and stimulating sites. Time line in milliseconds

In order to determine whether this distinctive potential was typical of the medial longitudinal fasciculus, the stimulating electrode was inserted in areas lateral to, medial to, and/or ventral to the medial and spinal vestibular nuclei or the medial longitudinal fasciculus. However, no characteristic potentials at the above voltage-duration settings could be elicited. Further, when the medial longitudinal fasciculus was sectioned at a site equidistant between the stimulating and recording sites, the evoked potentials disappeared (Fig. 3C).

Typical vestibulospinal responses in sulcomarginal bundle of ventral funiculus. Vestibulospinal evoked responses are characterized by a negative two-peak potential only on the ipsilateral side of the spinal cord (Fig. 4, Nos. 1-4). A single peak potential was always elicited on the contralateral side of the spinal cord (Fig. 5). These findings hold true for all spinal cord segments, cervical through sacral.

Starting just adjacent to the midline of the spinal cord, the recording electrodes were inserted ipsilaterally to within 0.5 mm. of the ventral limit of the anterior funiculus. This placed the first recording point in the ventral limit of the sulcomarginal bundle (Fig. 4, No. 1). After recording of the response at this point, the electrode was withdrawn and recordings were made at 0.5 mm. intervals until free of the cord (Fig. 4, Nos. 2-9). In this manner, multiple insertions of the recording electrodes were made, each insertion being

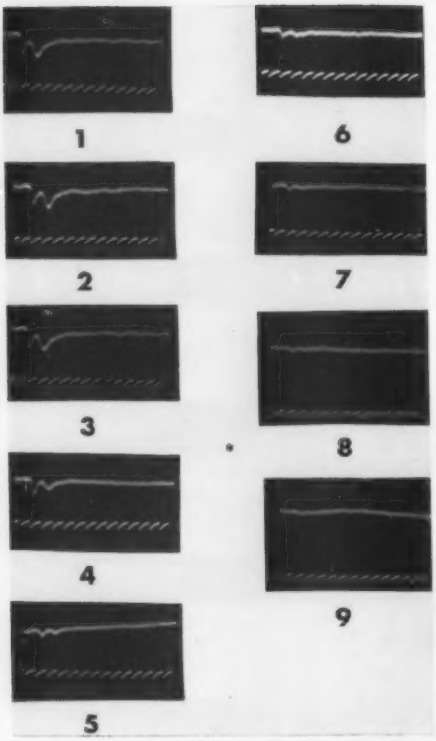


Fig. 4. Typical negative evoked potentials recorded in the ipsilateral sulcomarginal bundle in all segments of the spinal cord. Recording from within 0.5 mm. of the ventral limit of the sulcomarginal bundle [No. 1]. Numbers 2 through 9 illustrate potentials recorded during multiple withdrawals of the recording electrode at 0.5-mm. intervals until free of the cord.

about 1 mm. lateral to the previous insertion. Thus, one was able to map each segment of the cord (Fig. 1).

A negative double peak potential was evoked on the ipsilateral side of the cord. This response showed a latency of 1.5 msec. to the first negative peak, and 2 msec. to the second peak (Fig. 4). These typical responses were found at the second cervical segment of the spinal cord and maintained their characteristics throughout all segments of the spinal cord. A negative single peak response found on the contralateral side of the cord had approximately the same latency as the first peak of the double peak potential (Fig. 5). This typical potential was peculiar to all segments of the spinal cord and did not obviously change in latency, amplitude, or duration.

The double peak response gradually disappeared upon withdrawal at 0.5-mm. recording intervals as the electrode was elevated upward through the sulcomarginal bundle (Fig. 4). Likewise, the single negative peaks disappeared when the recording electrode was withdrawn from the sulcomarginal bundle of the contralateral side (Fig. 5). This yielded a

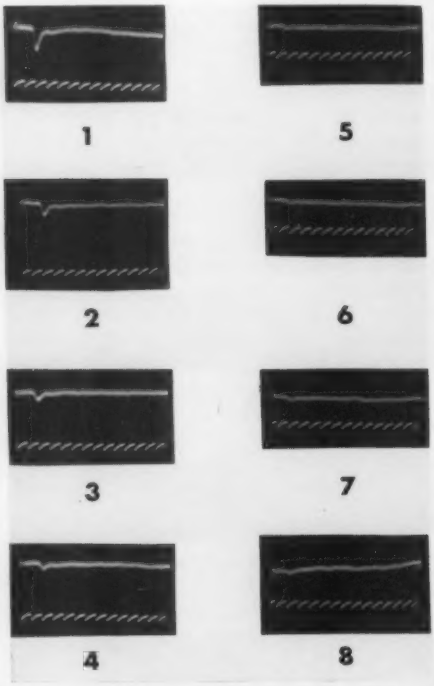


Fig. 5. Typical negative evoked potentials recorded in the contralateral sulcomarginal bundle in all segments of the spinal cord. Recording from within 0.5 mm. of the ventral limit of the sulcomarginal bundle [No. 1]. Numbers 2 through 9 illustrate potentials recorded during multiple insertions and withdrawals of recording electrode. Each potential [Nos. 1-8] taken at 0.5-mm. intervals during withdrawal

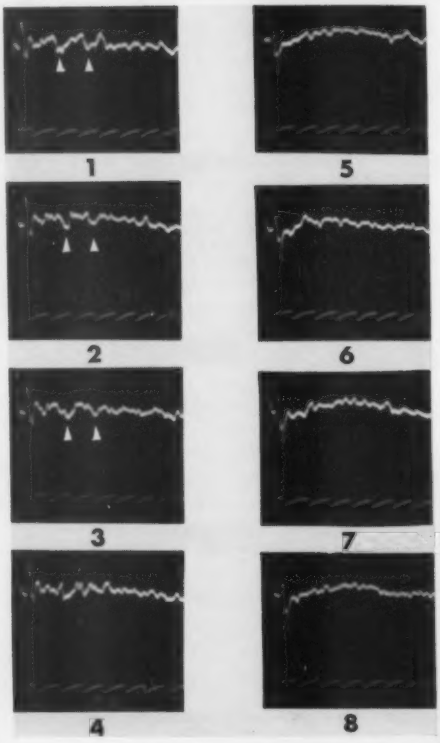


Fig. 6. Typical double peak negative responses seen routinely in the medial half of the anterior gray horn of all segments of the spinal cord. Number 1 is typical of the potential recorded near the ventral margin of the anterior gray horn. Numbers 2 through 8 are typical recordings observed in the medial half of the horn during withdrawal of the recording electrode at 0.5-mm. intervals.

fairly accurate map of the active areas in the sulcomarginal bundle of the spinal cord (Fig. 1). Hemisection or total transection of the spinal cord rostral to the recording points always abolished both the responses.

Characteristics of vestibular responses in ventral gray horn of spinal cord. The negative 2-peak response noted in the sulcomarginal bundle of the spinal cord also was characteristic, in an altered form, of the ipsilateral anterior gray horn of the spinal cord. The latency increased from that observed in the sulcomarginal bundle, from 1.5 msec., typical of the first peak, to 3 msec. Further, the latency to the second peak increased from 2 to 5 msec., while the amplitude remained relatively unchanged (Fig. 6).

The negative 2-peak potential again was peculiar only to the ipsilateral anterior gray horn (Fig. 7). In the contralateral gray horn, a single negative peak response was elicited. This peak also had a longer latency than that observed in the ipsilateral sulcomarginal bundle. Its latency increased from 1.5 to 3 msec., corresponding to the first peak in the 2-peak response.

These distinctive patterns of response were fraught with after potentials and spontaneous

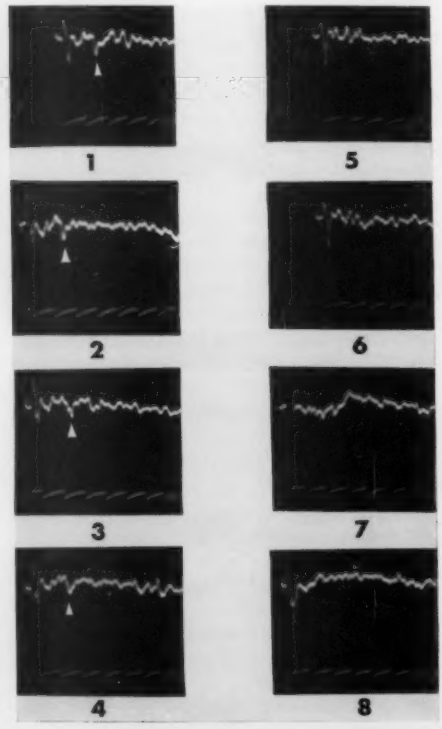


Fig. 7. Typical anterior horn responses recorded during withdrawal of recording electrode on the contralateral side in all segments of the spinal cord

firings characteristic of nuclear or cellular areas. Sometimes it was hard to determine the evoked potentials.

Multiple insertions and withdrawals of electrodes at 0.5-mm. intervals showed that these characteristic potentials were concentrated in the medial half of the anterior gray horn at all levels of the spinal cord. The lateral funiculi of both sides of the cord were completely negative (Fig. 1).

DISCUSSION

It has been stated in the results that a single, relatively slow, high amplitude response was recorded from points along the descending medial longitudinal fasciculus in the medulla oblongata during stimulation of either the medial or spinal vestibular nuclei. However, in recordings from the ipsilateral sulcomarginal bundle of any of the spinal cord segments, a two-peak response was found. A single peak response was noted on the contralateral side. These findings indicate that several factors influence the transmission of an impulse from the vestibular nuclei to the spinal cord. These are [1] an efferent or multisynaptic route via medullary reticular formation to the spinal cord, [2] an ascending afferent and a descending efferent system having different latencies activated through stimuli applied to the vestibular nuclei, and [3] a complex synaptic system within the vestibular nuclei connecting these nuclei via vestibulospinal systems with the spinal cord.

The first possibility mentioned above is borne out by the evidence accumulated in these experiments and the findings of other investigators.[18,19] The present findings correspond remarkably well with those recorded by Gernandt, Katsuki, and Livingston.[18] These authors found that single vestibular nerve shocks elicit a two-peak, motor neuron response that appears along both sides of the spinal cord. They postulate that impulses leading to the first peak undoubtedly descend in the vestibulospinal tract and probably connect monosynaptically with ventral horn cells. The second peak reaches the spinal cord via a reticulospinal system.

The results reported in this paper agree, in part, with the above statement. The exceptions lie in the two-peak response appearing along both sides of the spinal cord. Our findings indicate that the two-peak response is found only on the ipsilateral side. It is probable, however, that, if the vestibular nerve is stimulated, connections on both sides of the cord are activated by direct connections that may exist between the vestibular nerve ganglia and the medullary reticular formation. Such connections could activate a reticulospinal system not activated by stimulation of the medial or spinal vestibular nuclei and could account for the bilateral two-peak response.

Gernandt, Katsuki, and Livingston[18] also state that the second peak recorded in their observed response was carried to the spinal cord via a reticulospinal pathway. This concept is further supported by the work of Bach and Magoun,[20] in which they show that destruction of the vestibular nuclei after ablation of the pericruciate cortex reduces extensor rigidity. These two important reports certainly indicate a synergy existing between the reticulospinal system and the primary vestibulospinal system.

Our results show that the two-peak response associated with the vestibulospinal system may be accounted for, in part at least, by the two anatomically distinct vestibulospinal systems. It is well known that the vestibulospinal pathway is made up of two distinct systems.[3,6–8,12,13] It is possible, therefore, that the stimulus carried along the medial vestibulospinal tract accounts for one peak and the stimulus carried along the lateral vestibulospinal tract accounts for the other peak. It has not been established that the medial and spinal vestibular nuclei contribute fibers only to the medial longitudinal fasciculus.[6–8,12,13,21] However, it has been established that the lateral vestibular nucleus contributes fibers only to the lateral vestibulospinal tract.[12,13,21] Because of the overwhelming evidence indicating the complete separation of the actual tract systems associated with the vestibulospinal mechanism, the only possible association between the medial and lateral vestibulospinal tract systems could exist only in the vestibular nuclei complex.[1–13] On the basis of the above evidence, the first peak of our double peak response can be attributed to a potential carried by the medial vestibulospinal tract and can be traced directly to the single

peak response observed in recordings from the medial longitudinal fasciculus. Further support for this observation is lent by the fact that the first peak of the two-peak response corresponds in amplitude and latency to the first peak reported by Gernandt, Katsuki, and Livingston.[18] This, then, must be the monosynaptic vestibulospinal route mentioned by those authors.

It is somewhat more difficult to account for the second peak of the double peak response. Using the concepts reported by Lorente de No,[19] the second peak can be accounted for by a synaptic delay. Since the two descending vestibular fiber systems are distinct, this synaptic delay could occur at either the level of the vestibular nuclei or the level of the anterior motor horn cell of the spinal cord. It is probable that the delay observed to the second peak of a double peak response is due to a bisynaptic or multisynaptic junction existing either between the medial and/or spinal vestibular nuclei and the lateral vestibular nucleus or at the level of the anterior horn cells.

The fact that this two-peak response appeared on the ipsilateral side of the cord could be ascribed to fibers arising from the medial-spinal vestibular nuclei complex and the lateral vestibular nucleus. Near the extreme caudal medulla oblongata, these fibers intermingle and enter the sulcomarginal bundle in the cervical spinal cord. As reported previously by Massopust,[22] the fibers are then distributed to cells of the medial half of the anterior gray horn in all segments of the spinal cord. Attempts to examine the source of delay between the two peaks of the double response were unsuccessful because stimulation of medullary areas occupied by the lateral vestibulospinal tract also activated other reticulospinal pathways, which confused the picture.

Szentogothai-Schimert[10] and Pompeiano and Brodal[12,13] have demonstrated a preponderance of large-caliber fibers existing in the medial longitudinal fasciculus, while the lateral vestibulospinal tract contains medium-diameter fibers. From the above caliber determinations, one might speculate on the differences in latency of the two peaks. This latency difference could be due to the variation in conduction velocity of the large and small diameter fibers; however, it is uncertain which fiber system contributes to such a difference in velocity. Evidently, no cross connections exist between the medial and spinal vestibular nuclei of opposite sides, as evidenced by the single peak potential appearing on the contralateral side of the cord.

The second possible connection of the vestibular nuclei with the spinal cord is the possible existence of an uncrossed afferent system linking the spinal cord with the vestibular nuclei. Stimulation of the medial and spinal vestibular nuclei could activate both the above systems, causing the two-peak response. Evidence obtained by Lloyd[23] and Pompeiano and Brodal[12,13] indicates that the existence of an afferent system directly connecting the spinal cord with the medial and spinal vestibular nuclei is unlikely; therefore, we did not further examine this possibility.

As far as the third possibility is concerned, the findings of Lorente de No,[19] French, Verzeano, and Magoun,[24] and Gernandt, Katsuki, and Livingston[18] largely eliminate the possibility that a complex circuit exists within the vestibular nuclei themselves.

On the basis of the findings in these experiments and the previous evidence in the literature, it is postulated that the ipsilateral two-peak response found on stimulation of the medial and spinal vestibular nuclei was due to monosynaptic potentials being carried by the medial vestibulospinal tract and some other descending system. The first peak of the two-peak response was carried monosynaptically to the anterior horn cells of the spinal cord via the descending medial longitudinal fasciculus and sulcomarginal bundle. The second peak was transmitted multisynaptically to the same areas of the spinal cord by the lateral vestibulospinal tract. The delay observed between the first and second peak was probably due to a synaptic junction possibly existing between the medial-spinal vestibular nuclei and the lateral vestibular nucleus, a reticular nucleus, or the cells of the anterior horns of the spinal cord. The descending tract, whatever it may be, is uncrossed, since only the first peak was observed on the contralateral side of the cord.

Further studies are planned in an attempt to establish the tract system responsible for

contributing one or the other peak in the two-peak response.

SUMMARY

Bipolar stimulation of the medial and spinal vestibular nuclei evoked a single negative, relatively slow, peak response that was distinctive in both the ipsilateral and contralateral bundles of the descending medial longitudinal fasciculus.

In the spinal cord, a two-peak response was elicited during stimulation of the above nuclei on the ipsilateral side of all segments of the spinal cord. A single peak potential was peculiar to the contralateral side. These responses were found only in the sulcomarginal bundle and the medial half of the anterior gray horn in all segments of the spinal cord.

Section of either the medial longitudinal fasciculus or spinal cord above the recording electrode sites abolished both types of responses.

The anatomicophysiologic implications of the above findings are discussed.

The author wishes to thank Mrs. Betty Anderson for preparation of the histologic material and Mr. Harold Hambrick for the photography.

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Progressive ataxia in childhood with particular reference to ataxia-telangiectasia

Robert P. Sedgwick, M.D., and Elena Boder, M.D.

In the differential diagnosis of ataxia in children, one must decide, from history and observation, whether the ataxia is acute and transitory, relatively fixed, or progressive in severity. The acute transitory group is usually of toxic or infectious origin. If no etiology can be found, the condition may be diagnosed "acute cerebellar syndrome of childhood."[1,2] If the ataxia is relatively fixed, various prenatal, natal, or postnatal conditions, such as anoxia, trauma, vascular accident, or infection, must be considered and diagnoses such as "cerebellar hypoplasia" or "ataxic cerebral palsy" may be made.

If the ataxia is progressive, the first consideration must be posterior fossa neoplasm. Also, structural abnormalities in the posterior fossa, foramen magnum, and cervical spine with concomitant neural defects may result in progressive ataxia.[3] If these conditions are ruled out, the progressive ataxia is probably due to metabolic-degenerative disease.

Ataxia and pathologic changes in the cerebellum have been noted in a wide variety of diffuse central nervous system disorders of progressive type.[4,5] Such disease may involve primarily either gray or white matter. Examples of such disorders would include tuberous sclerosis[6] and the cerebral scleroses such as Schilder's disease and Pelizaeus-Merzbacher disease. The cerebral lipoidoses, including the familial amaurotic idiocy group and Alper's degeneration of the cerebral gray matter, could also be included here.[7,8] It is rare, however, that ataxia remains as a primary and isolated symptom in these diseases, and widespread neurologic deficit soon makes itself apparent.

Further considerations include the system degenerations involving the cerebellum and its afferent and efferent tracts. These disorders are often heredofamilial. The classic example of such a disorder in children is, of course, Friedreich's ataxia.[9] There are numerous variants and formes frustes of this disease, but it is in general a well delineated clinical entity and easily recognized by its classic features: hereditary transmission, onset between 6 and 18 years, ataxia of trunk and intention, kyphoscoliosis and typical foot deformity, posterolateral column signs, diminished or absent tendon reflexes, hypotonia, occasional optic atrophy and heart disease, and definite, although usually slow, progression.[9–12]

If the child does not fit into the Friedreich group, there may be difficulty in making a diagnosis other than the unsatisfactory one of "progressive ataxia of childhood." It is best, then, to describe the patient as exhaustively as possible according to some precise scheme such as that presented by Lichtenstein.[13] Batten[14] in 1905 stressed the difficulty of diagnosis in cases "in which a child has been healthy until a certain age, and then has gradually developed ataxia; cases in some points resembling Friedreich's disease, but differing from the classical picture of that disease." The present study was undertaken to ascertain what clinical entities other than Friedreich's ataxia characteristically give rise to chronic progressive ataxia in childhood.

ATAXIA-TELANGIECTASIA

The authors' interest in this problem was aroused by the study of 8 children from 5 nonrelated families with chronic, primary, and

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TABLE 1
SUMMARY OF KNOWN CASES OF ATAXIA-TELANGIECTASIA

Authors	Year	Cases (No.)	Age* (Years)	Necropsy (No.)
A. *Published Cases*				
Louis-Bar[18]	1941	1	9	
Boder and Sedgwick[15,16]	1957	8†	6–25	1
Wells and Shy[19]	1957	2	9, 10	
Biemond[20,21]	1957	4	9–17	2
Centerwall and Miller[17]	1958	2	8–12	1
B. *Unpublished Cases*				
Buchanan[22]	1956	3	10–14	
Ford[24]	1957	1	6	
Perlstein[26]	1957-59	2	6, 12	
Centerwall[27]	1958	1	23	1
Phelps[27]	1958	1	10	
Pickup[28]	1958	2	9, 14	
Smith and Cogan[29]	1958	1	18	
Boder and Sedgwick[30]	1959	3	3–10	1
Hughes[25]	1959	1	4	
		31		6

*Age at diagnosis or at death
†One patient is reported with necropsy by Centerwall and Miller.[17]

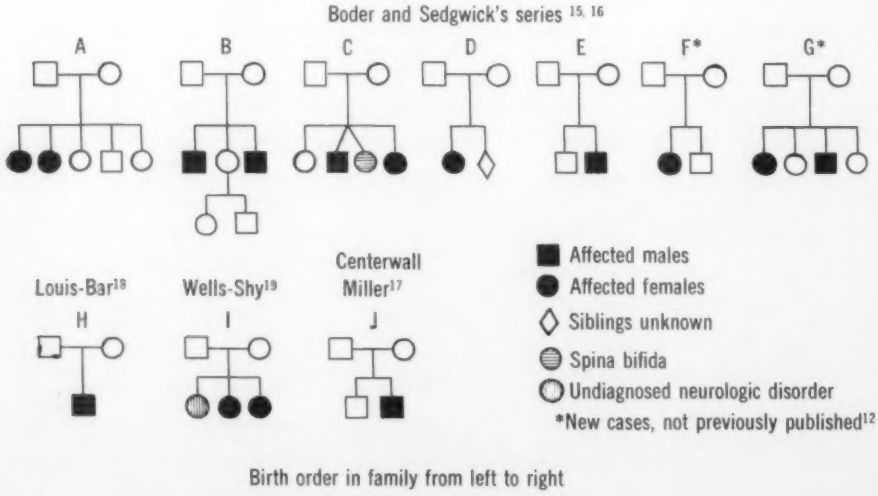

Fig. 1. Familial occurrence of ataxia-telangiectasia in published cases

Fig. 2. Characteristic telangiectases of the bulbar conjunctivae in a child aged 9 years

Fig. 3. Child aged 7 years with characteristic telangiectasia of the bulbar conjunctivae and butterfly area of the face, especially the bridge of the nose. Note fading out at the cornea and symmetric distribution. (Courtesy of the *University of Southern California Medical Bulletin*[15])

progressive ataxia who seemed to have such similarity of symptoms, findings, and course as to justify their inclusion into a syndrome entity easily differentiated from Friedreich's ataxia. In reporting this work, the authors have named the syndrome "ataxia-telangiectasia" (A-T) from the 2 main features of the syndrome: progressive ataxia and oculocutaneous telangiectasia.[15,16] In addition to the authors' cases, 4 others have been published[17–19] and 4 more were reported at the First International Congress of the Neurological Sciences at Brussels in July 1957.[20,21] From personal communications[22–29] and other cases seen but as yet unpublished,[30] the authors have become aware of 15 more such patients, making a total of 31 known cases with this syndrome (Table 1).

Ataxia-telangiectasia is a familial syndrome; the mode of inheritance is apparently mendelian-recessive, since there are as yet no known instances of an affected child having a similarly affected parent (Fig. 1). *Ataxia* is the first symptom and has its onset in infancy, becoming manifest at the time the child starts to walk. The ataxia is of cerebellar type and affects station, gait, and intention. There are no clinical or pathologic findings definitely implicating the posterior columns, thus separating these patients from those with spinal ataxia. The ataxia is steadily progressive, so that most of the patients are confined to wheel chairs before adolescence. The *telangiectasia* has later onset and usually appears from age 4 to 6 years [15–17] (Figs. 2, 3, and 4). It

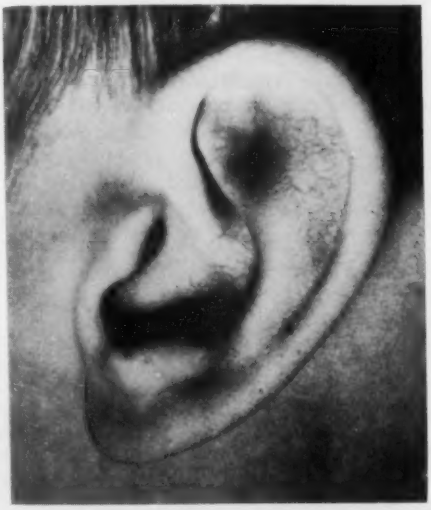

Fig. 4. Faint hairline telangiectases on the external ear in a child aged 10 years

TABLE 2
CLINICAL FEATURES IN 31 CASES OF ATAXIA-TELANGIECTASIA

Feature	*Cases with information available (No.)*	*Cases with feature (No.)*	*Cases with feature (%)*
Neurologic features			
Cerebellar ataxia, onset in infancy or childhood	31	31	100
Diminished or absent deep reflexes	17	14	82
Flexor or equivocal plantar response	17	17	100
Negative Romberg's sign	13	11	85
Intact deep and superficial sensation	16	16	100
Choreoathetosis	20	15	75
Oculomotor signs			
Peculiarity of eye movements	15	12	80
Fixation nystagmus	17	14	82
Dysarthric speech	23	23	100
Drooling	14	13	93
Characteristic facies and postural attitudes	17	17	100
Telangiectasia, oculocutaneous	30	30	100
Frequent sinopulmonary infection	21	17	81
Familial occurrence	30	18	60
Equable disposition	12	12	100
Mental deficiency	21	6	29
Retardation of statural growth	18	12	67
Changes of hair and skin	13	11	85

spreads in characteristic fashion. The exposed bulbar conjunctivae are first affected, causing what is usually considered to be conjunctivitis or pink eye. The telangiectasia then spreads to involve the butterfly area of the face, external ears, palate, creases and V of the neck, and, finally, the antecubital and popliteal fossae and dorsum of the hands and feet.[15–17,19,20] This telangiectasia is primarily arterial.[31,32]

A third prominent feature of the syndrome is frequent otic and sinopulmonary infections that may progress to chronic bronchitis and bronchiectasis.[15–17,20] The reason for this is not clear, since in the limited autopsy material available no gross vascular or parenchymal anomaly in the lungs has been found.[15–17,20]

A fourth feature is a peculiarity of eye movements difficult to classify. Eye movements may be initiated with difficulty, are often jerky during their excursion, and may halt before movement is completed. On fixation, the eyes may show fixation nystagmus. The lids may blink spasmodically during movement of the eyes.[15,16] According to Cogan,[33] this resembles the Roth-Bielschowsky phenomenon in that the difficulties are observed only on voluntary and not on reflex gaze.

Other but less striking elements of ataxia-telangiectasia are characteristic facies, equable disposition, cerebellar speech, drooling, variable choreoathetoid movements and posturing, occasional myoclonic jerks, absence of mental deterioration as a characteristic symptom, and retardation of statural growth[15–20] (Table 2).

Skull roentgenograms, spinal fluid study, blood count, urinalysis, and electroencephalograms have not revealed any consistent deviation from normal;[15–17,19] 3 out of 4 pneumoencephalograms have shown cerebellar atrophy.[15–17] Serum and urine studies of iron, copper, and lead have not revealed any abnormality.[15,16,19] Electrophoretic studies of serum in 2 patients have demonstrated that concentrations of gamma globulin are normal;[15,16] 4 necropsy reports have been published,[15–17,20] and all provide microscopic evidence of apparently primary, chronic, diffuse cortical cerebellar degeneration, chiefly affecting the Pur-

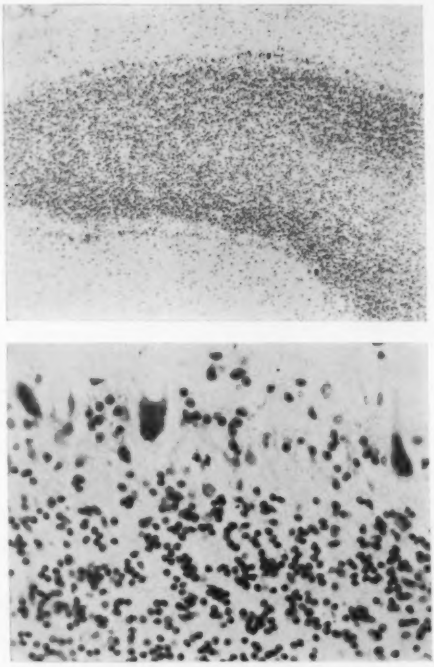

Fig. 5. Section through cerebellar folia. (*Top*) Note paucity of Purkinje cells and thinning of the granular layer. Nissl body stain. × 55. (*Bottom*) Chronic nerve cell change in the Purkinje cells. Nissl body stain. × 250. (L.Z., Case 1[15,16])

kinje cells but also the granule cells and the basket cells (Figs. 5 and 6). The white matter of the cerebellum is relatively spared (Fig. 7). Secondary and minor changes may also be noted in the neuronal elements of the dentate and olivary nuclei. The remainder of the brain stem, basal ganglia, cerebral cortex, and white matter are relatively uninvolved. The question of vascular pathology in the central nervous system is not settled. In 2 cases, microscopic examination of the venules of the meninges and cerebellar white matter showed them to be enlarged and perhaps more numerous than normal.[15–17] Myelin sheath sections of the spinal cord do not show significant demyelinization (Fig. 8).[15,16]

The course of ataxia-telangiectasia is one of

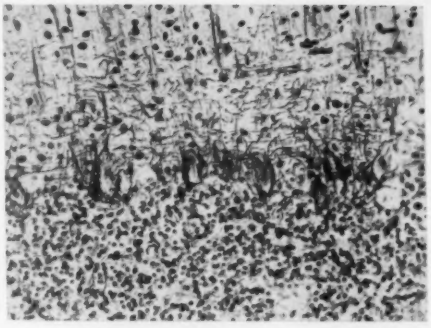

Fig. 6. Section showing degeneration of baskets. Cajal's reduced silver. × 250

Fig. 7. Section through the white matter of the cerebellum showing relative preservation of the myelin sheaths. Myelin stain. × 30

slow but relentless progression. The longest known survival has been to the age of 25 years.[15,16] Treatment consists of physical therapy, rehabilitative procedures, and appropriate antibiotic medication for pulmonary infections. Recognition of the syndrome will eliminate

Fig. 8. Section through the spinal cord showing relative preservation of gray and white matter. Myelin sheath stain. × 6

unrewarding diagnostic procedures such as air study and posterior fossa exploration.

To study the problem of progressive ataxia in children still further, the pertinent literature and clinical records of ataxic children at Los Angeles Children's Hospital were reviewed.

REVIEW OF CASES

The authors have examined the charts of all patients admitted to Los Angeles Children's Hospital since 1950 who fell into one of the following groups: [1] those with chronic nervous system disease (excluding tumors); [2] those given a symptom diagnosis of "ataxia;" [3] those with a diagnosis of "benign" or "infectious" ataxia of childhood; and [4] those with a diagnosis of "ataxic cerebral palsy." Since 1950, 222 patients had significant ataxia due to nonneoplastic disease (Table 3).

The diagnoses listed in Table 3 are derived from review of the hospital charts rather than solely from the discharge diagnoses. Diagnoses were assigned on a lenient basis of sufficiently reasonable rather than according to strict diagnostic criteria, since, if the latter method had been used, a high proportion of the patients would have remained, of course, without diagnoses. None of the totals in Table 3 have any significance as far as absolute incidence is concerned. Los Angeles Children's Hospital serves primarily the acutely ill and also has served as a diagnostic center for the State cerebral palsy program. The population studied is therefore a selected one. It also should be noted that, since this is a study of chronic progressive ataxia, the number of cases in groups 1 and 2 have no relevance here except to show the source and number in the total sample and to give some idea of the relative incidence of these groups at Los Angeles Children's Hospital over the period of study.

The "undiagnosed" patients were not observed for a sufficient length of time or did not have sufficient specificity of history or findings to reasonably assign them to any diagnostic category. In none of the patients labeled "probable progressive neuronal disease" was the ataxia an isolated and primary symptom for very long; dementia, spasticity, blindness, and seizures as well as prominent extrapyramidal symptomatology soon differentiated them from those with system degeneration. Illustrative of this is a child of 3 years observed for about two years. His first symptom was ataxia, but soon he displayed a severe convulsive disorder with both major seizures and myoclonic jerks, mental deterioration, bulbar signs, and flaccid quadriplegia; these were followed by stupor, coma, and death. The child exhibited prominent pyramidal signs as well as ataxia and optic atrophy. Skull films and cerebrospinal fluid were normal, but the electroencephalogram showed a severe and diffuse slow wave abnormality. At autopsy, there was diffuse softening of the entire cerebral cortex as well as a somewhat shrunken cerebellum. The microscopic findings are not yet available. The gross pathologic diagnosis was laminar cortical necrosis.

Table 4 compares the clinical features of the 15 cases of Friedreich's ataxia with the 7

TABLE 3
CLASSIFICATION OF 222 PATIENTS WITH SIGNIFICANT ATAXIA
Los Angeles Children's Hospital, 1950-1958

1. "Ataxic cerebral palsy"		147
2. Acute cerebellar syndrome with recovery (toxic, infectious)		46
3. Chronic progressive ataxia		29
a. Friedreich's ataxia	15	
b. Ataxia-telangiectasia	7	
c. Probable progressive neuronal disease (2 with myoclonic seizures)	3	
d. Basilar arachnoiditis with hydrocephalus	1	
e. Undiagnosed	3	

TABLE 4
COMPARISON OF 15 CASES OF FRIEDREICH'S ATAXIA WITH 7 CASES OF ATAXIA-TELANGIECTASIA

Feature	*Friedreich's ataxia* (15)	*A-T* (7)
1. Evidence of hereditary transmission	10	6
2. Onset prior to age 4 years	1*	7
3. Signs of posterior column deficit	9	0
4. Signs of pyramidal deficit	8	0
5. Choreoathetosis	0	5
6. Diminution or absence of deep reflexes	14	7
7. Kyphoscoliosis and/or typical foot deformity	9	0
8. Cutaneous stigmata	0	7
9. Frequent sinopulmonary infections	0	6
10. Optic atrophy	0	0
11. Evidence of heart disease	2	0
12. Telangiectasia, oculocutaneous	0	7

*In 5 cases onset was dated only to "childhood."

cases of ataxia-telangiectasia found in this study.

REVIEW OF LITERATURE

The extensive literature concerning heredoataxia is difficult to evaluate for several reasons:[13,34] [1] extensive use of eponyms after afflicted families and reporting investigators; [2] the profusion of reports of "intermediate forms" describing syndrome variants or association of 2 syndromes (the papers of Roth[35] and Schut and Haymaker[36] analyze this problem and show how genetic factors cut across clinical lines); and [3] the necessity still of classifying along lines of clinical and pathologic interpretation and description rather than according to demonstrable metabolic defect. Fortunately, the recent publication of Greenfield's monograph[12] and Dow and Moruzzi's textbook[7] provides judicious selection of the important literature, with concise tabular analyses of pertinent data from the important series and a workable scheme of classification.

Greenfield's anatomic classification[12] is shown in Table 5 in slightly modified form and the usual and earliest ages of onset have been noted. The figures given are taken largely from Greenfield's tabular analyses and text. The anatomic order shown in the classification will be followed in this discussion.

Under "predominantly spinal forms," Greenfield places Friedreich's ataxia and "hereditary spastic ataxia," including the variants indicated. It will be noted that, while Friedreich's ataxia may occasionally have its onset in early childhood, it is usually first symptomatic in preadolescence or adolescence. Patients assigned to the hereditary spastic ataxia group are those who have demonstrated, both clinically and pathologically, a spinal type of ataxia differing from that of Friedreich by a later onset, increased deep reflexes, and absence of the characteristic skeletal stigmata. The name Marie's ataxia has been widely used in connection with this group.[12]

The "spinocerebellar forms" include type A (Menzel), which is Greenfield's designation for a group of cases of hereditary ataxia characterized both clinically and pathologically by spinal as well as olivary, pontine, and cerebellar degeneration. Onset in this group is in middle adult life.

The "predominantly cerebellar forms" include type B (Holmes[37]), olivopontocerebellar atrophy, and dentatorubral atrophy. No childhood cases of the first 2 types are recorded by Greenfield, but dentatorubral atrophy requires further consideration.[38] One of Hunt's patients had onset of myoclonus at the age of 7 years.[39] Malamud and Cohen[40] have recently described a child whose illness began at about 10 months and who died at the age of 7 years. Pathologic examination revealed

TABLE 5
THE SPINOCEREBELLAR DEGENERATIONS*

Type	*Onset (years) Usual*	*Earliest*
A. *Predominantly spinal forms*		
1. Friedreich's ataxia, including cases associated with Charcot-Marie-Tooth disease and the Roussy-Levy syndrome	10-13	3
2. Hereditary spastic ataxia, including certain of Marie's families and those of Sanger-Brown, Fraser, Nonne, and Klippel and Durante	20-40	10(?)
B. *Spinocerebellar forms*		
1. Type A (Menzel)	38 (mean)	14
2. Subacute spinocerebellar degeneration (carcinogenic and sporadic)	—	—
C. *Predominantly cerebellar forms*		
1. Type B (Holmes)	45.5(mean)	27
2. Olivopontocerebellar atrophy	"Late middle life"	
3. Dentatorubral atrophy, including the Ramsay Hunt syndrome	?	?

*Modified from Greenfield

marked degenerative changes in Purkinje cells, dentate nucleus, superior peduncles, olivary bodies, basal ganglia, and thalamus. Despite such case reports, however, the evidence for the existence of an isolated atrophy of the cerebellar nuclei is not very great.[7] Greenfield adds, "No case of severe bilateral degeneration of the nucleus dentatus, and superior peduncle, without degeneration of other spino-cerebellar systems, has come to light in an extensive survey of the literature." The whole question, therefore, of whether there exists an entity of dentatorubral atrophy and, if so, whether it occurs in children must remain open for the present.

Dow and Moruzzi[7] have discussed briefly the reports of hereditary cortical cerebellar atrophy occurring in infants.[14,41–43] Study reveals that these are all descriptions of 1 or 2 families only. The pathology in the cases of Jervis[41] and Norman[42] consisted primarily of degeneration of granular rather than Purkinje cells. Dow and Moruzzi have concluded that, while cases of cortical cerebellar atrophy have been described in children, they are less clearly defined than those occurring in adult life.

Garland and Moorehouse[44] have reported 2 siblings suffering from a rare (20 known cases) hereditary syndrome consisting of cerebellar ataxia, oligophrenia, cataract, pyramidal signs, and growth retardation. Baron and associates[45] have described a family (Hartnup) in which 4 of 8 siblings had transient pellagra-like skin rash, aminoaciduria, and recurrent cerebellar ataxia precipitated by sunlight. An endemic disease, kuru, occurring in New Guinea, has recently been described by Gadjusek and Zigas.[46] This rapidly fatal disorder affects the central nervous system widely and is clearly not a system degeneration on either clinical or pathologic grounds. One feature of the disease, however, is progressive ataxia.

The association of cerebellar and extrapyramidal symptomatology is not uncommon.[12] Malamud and Cohen[40] cite Rosenhagen's[47] series of 45 patients with cerebellar ataxia, 25 of whom displayed extrapyramidal signs. There is conflicting opinion as to whether isolated dentate atrophy can be the pathologic basis for an extrapyramidal syndrome or whether there must always be an associated lesion of the basal ganglia.[7,40]

DISCUSSION

This study has been undertaken in order to answer the question: What are the spinal, spinocerebellar, or cerebellar system degenerations of childhood which produce primary, chronic, and progressive ataxia? The term system degeneration is used here in the conventional way and implies that one neural system degenerates progressively and that this results in a fairly characteristic train of symptoms. None of these system degenerations are pure as a rule, and other parts of the nervous system may be affected, although in less characteristic and severe fashion. Such a definition excludes those diseases affecting white or gray matter diffusely, such as amaurotic family idiocy, Schilder's disease, and Wilson's disease, which may give rise to ataxia in children as either a presenting major symptom or a late minor symptom. Usually, the diffuse degenerations, in contrast to the system degenerations, will soon make themselves known by widespread and devastating deficit affecting multiple neural systems. One should not, of course, attempt to adhere to this division too rigidly, since there are many borderline cases and system degenerations can be quite diffuse; diffuse degenerations may, early in their history, affect primarily one or two systems. Indeed, ataxia-telangiectasia may be more diffuse than the authors have previously considered, since there is clinical evidence implicating the cortex and basal ganglia as well as the cerebellum. Nevertheless, in the main, the differentiation seems valid.

Friedreich's ataxia is clearly the most common spinocerebellar system degeneration of childhood. It is the authors' opinion that there is now sufficient clinical and pathologic evidence to support the statement that ataxia-telangiectasia is another member of this group.

It is possible that dentatorubral atrophy of childhood will emerge as a third distinct progressive cerebellar syndrome of childhood and that such cases will be clinically recognized by the coincidence of progressive ataxia and myoclonus epilepsy as suggested by Ramsay Hunt[39] many years ago. There is as yet, however, insufficient clinical and pathologic evidence to state that such an entity exists.

Lastly, there have been case reports of children who suffer from progressive ataxia and

yet do not fall into any of these three groups. They seem to have no identifying feature, other than their ataxia, that would enable one to isolate a number of them as a group for study. The illness of such children can only be labeled at the present time "progressive ataxia of childhood."

Following Greenfield's[12] classification of spinocerebellar degenerations, ataxia-telangiectasia would definitely fall under the heading of "predominantly cerebellar form." It differs clinically, however, from the other types listed, since in none of them is the onset in infancy or early childhood nor are there associated telangiectasia and proneness to sinopulmonary infections including bronchiectasis.

Ataxia-telangiectasia also differs from Friedreich's ataxia in many important features: [1] earlier onset; [2] characteristic oculocutaneous telangiectasia; [3] frequency of sinopulmonary infections; [4] absence of posterior column deficit; [5] relative absence of pyramidal signs; [6] absence of kyphoscoliosis and foot deformity; and [7] pathologic evidence that ataxia-telangiectasia is primarily a degeneration of the cerebellar cortex as opposed to the primary spinal degeneration seen in Friedreich's ataxia. It might also be pointed out that, as far as the authors know, ataxia-telangiectasia is the only progressive cerebellar ataxia thus far described which consistently has its onset in infancy.

Ataxia-telangiectasia also may be properly classified in the group of neuroectodermoses or *phakomatoses,* which at present include neurofibromatosis (von Recklinghausen's disease), tuberous sclerosis, von Hippel-Lindau disease, and Sturge-Weber syndrome, since it combines oculocutaneous vascular abnormality with central nervous system disease.[48–50] The similarity of ataxia-telangiectasia to von Hippel-Lindau disease is only superficial, since the ocular lesion of the latter is angiomatosis retinae rather than conjunctival telangiectasia and the cerebellar lesion is an angiomatous malformation or hemangioblastoma rather than cerebellar cortical atrophy.[4,15–17,20] Ataxia-telangiectasia differs from Rendu-Osler-Weber disease in that the characteristic telangiectases in the latter are different in appearance and distribution and have definite bleeding tendencies, which are absent in ataxia-telangiectasia; also, no instances of cerebellar atrophy associated with Rendu-Osler-Weber disease have been reported.

SUMMARY AND CONCLUSIONS

The progressive ataxias of childhood (excluding those due to neoplasm) have been studied by means of review of hospital records and the pertinent literature.

Of the spinocerebellar degenerations occurring in childhood, 2 distinct entities stand out. The first, Friedreich's ataxia, typically starts between 6 and 15 years of age. The second, ataxia-telangiectasia, consistently begins in infancy and early childhood.

Other such degenerations occurring in childhood are poorly defined and can be diagnosed at present only as "progressive ataxia of childhood;" this latter also may be symptomatic of more diffuse central nervous system disorders involving white or gray matter and thus will be accompanied by other symptoms and signs of severe neural deficit.

Ataxia-telangiectasia can be differentiated from Friedreich's ataxia by the presence of typical oculocutaneous telangiectasia, frequent sinopulmonary infections including bronchiectasis, and the absence of posterolateral column signs, kyphoscoliosis, and foot deformity. It is a "predominantly cerebellar form" of heredoataxia, whereas Friedreich's ataxia is a "predominantly spinal form," following Greenfield's classification of spinocerebellar degeneration. It appears to be the only well defined entity of predominantly cerebellar degeneration of infancy and childhood so far described. It also may be considered as a fifth member of the group of phakomatoses.

The clinician's ability to identify early cases of ataxia in children as being Friedreich's ataxia or ataxia-telangiectasia will eliminate the painful and sometimes dangerous procedures of air study and posterior fossa exploration for neoplasm.

The authors wish to express their appreciation to Dr. Emil Bogen for his thoughtful criticism of this paper.

ADDENDUM

Since submitting this paper for publication, ataxia-telangiectasia has been included in the recent book by Durham entitled, *Encyclopedia of Medical Syndromes.*[51]

The reports of Biemond and van Bolhuis[52]

and Smith and Cogan,[53] whose patients are cited in Table 1, have been published. In addition, 3 new papers[54–56] on the syndrome, based on 5 more cases, and 2 critical reviews[57,58] have been published.

Our own experience with the syndrome has grown with observations on a new patient, made possible through the courtesy of Dr. James L. Caffee of Fresno, Calif.[59] This patient, whose sibling died of a similar disorder, brought the total number of cases carefully studied by us to 13,[15,16,30,60] which includes 3 necropsies.

From personal communication with other physicians[22–28,61–65] and from the literature [15–20,52–56] we now have data on a total of 52 known cases, including our series of 13, suggesting that the ataxia-telangiectasia syndrome may not be as rare in incidence as we originally believed.

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BOOK REVIEWS

Encyclopedia of Medical Syndromes

by Robert H. Durham, M.D., 628 pp., Paul B. Hoeber, Inc., New York. $13.50

Until the appearance of this book, there was no complete encyclopedic reference text of eponymic and descriptive syndromes available in the English language. Perhaps one might say that medicine has too many syndromes and that each syndrome has too many synonyms. Nevertheless, syndromes have become an important part of medicine, and, if one is to use them in diagnosis and classification, one should be certain of their meanings; with many, the accepted usage varies considerably from the original descriptions.

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R.N.D.

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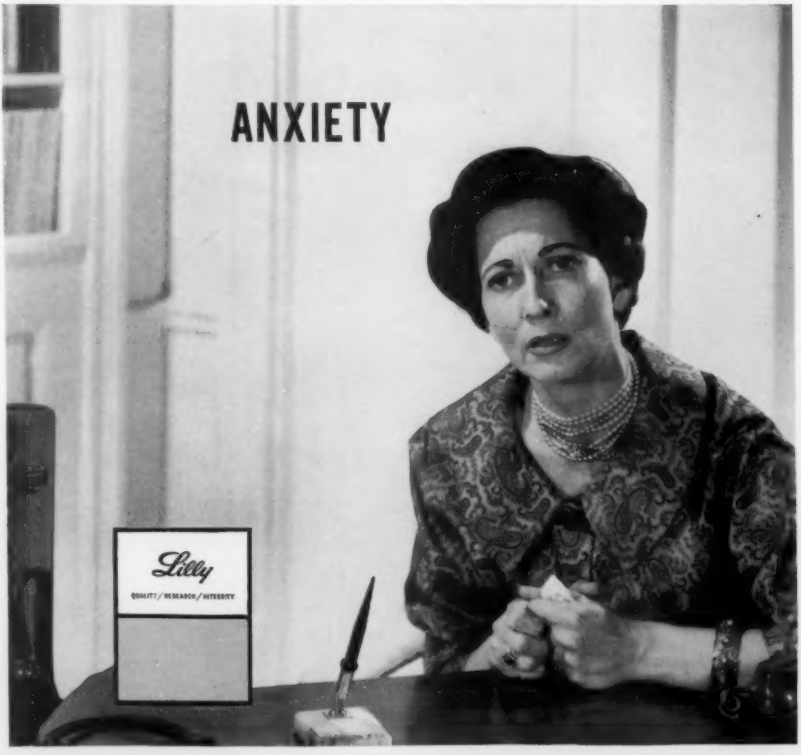

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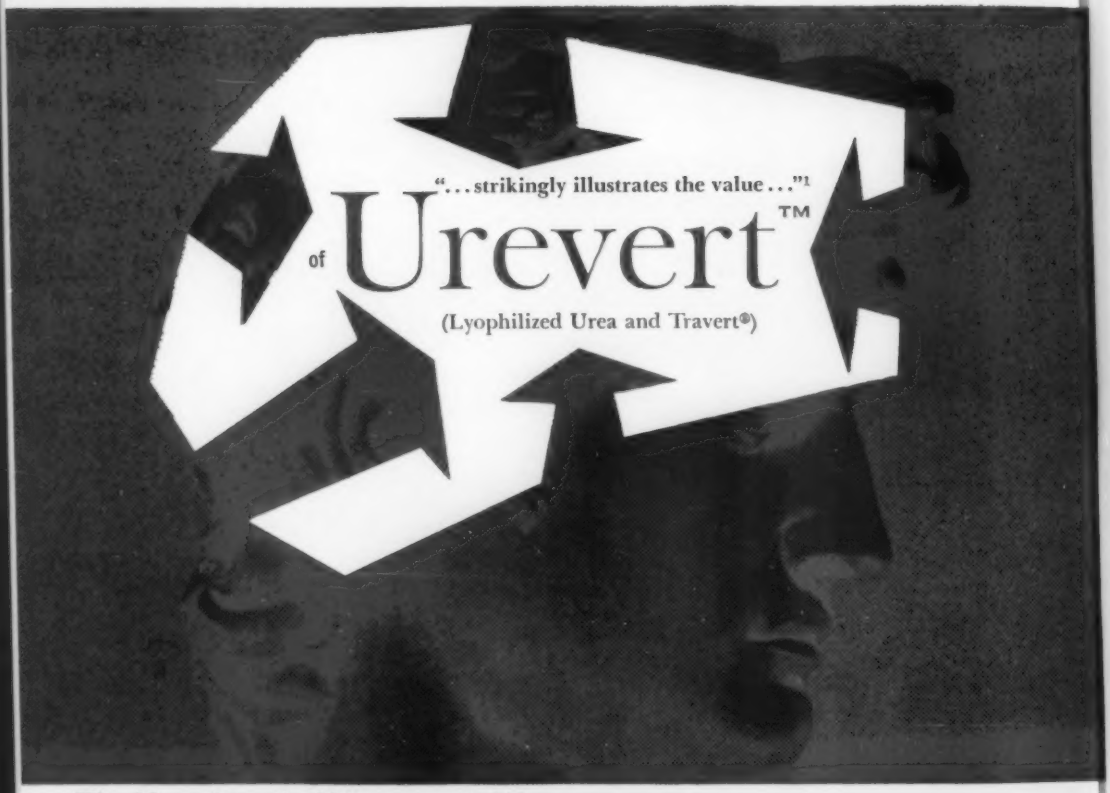

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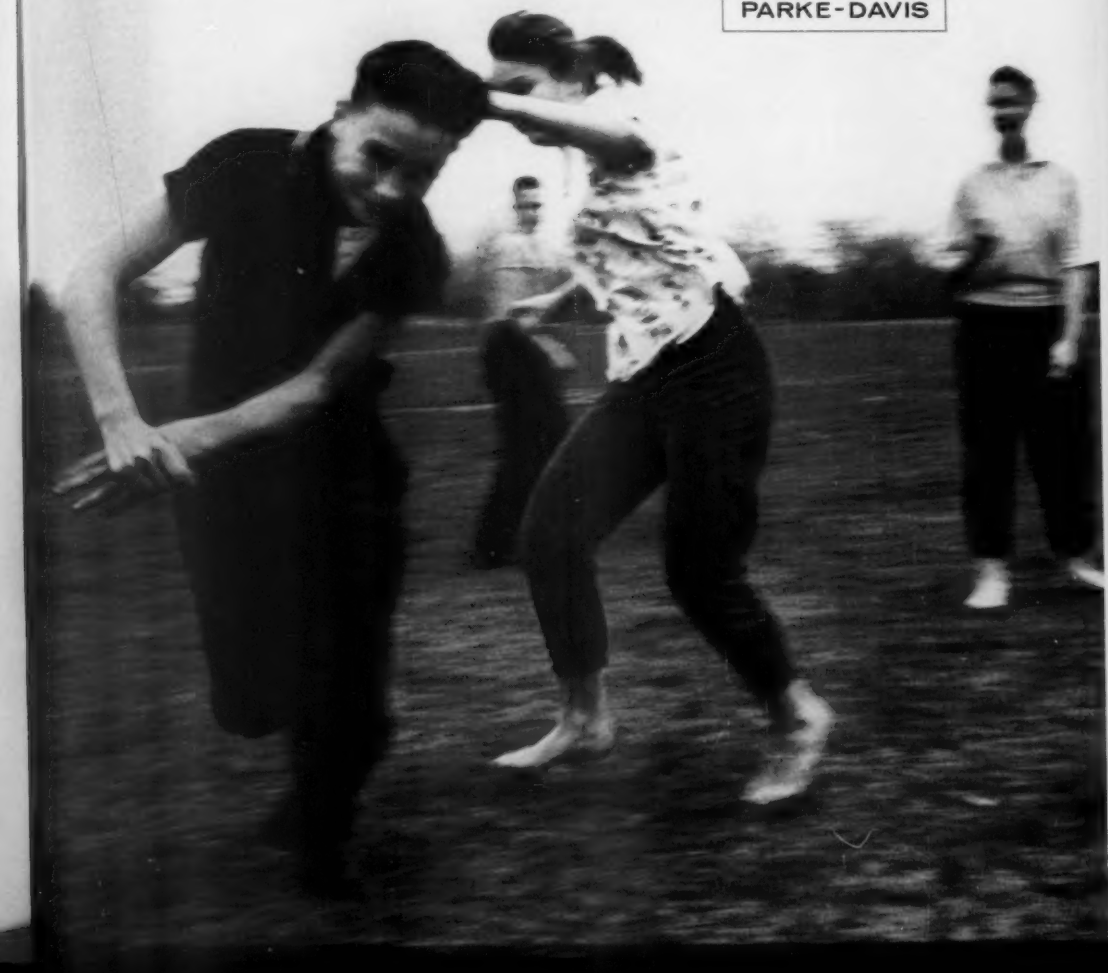

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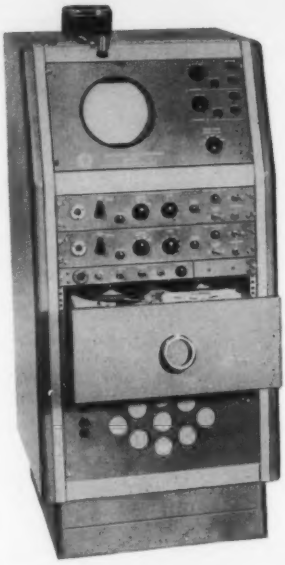

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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

JULY 1960

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Special Courses Reach New High at Miami Meeting

A. B. Baker's battery of special refresher courses in basic and clinical neurology reached a new peak of success in both quality and attendance at the Annual AAN Meeting in the Eden Roc Hotel, Miami Beach, April 25 through 30; 296 neurologists and neurologic scientists registered for 649 individual courses. Topping the list in popularity was the course in child neurology with 126 registrants (Paul M. Ellwood); next came the course in electroencephalography with 97 registrants (Frank Morrell), neurologic aspects of internal disease with 89 (Gilbert H. Glaser), genetics with 69 (Leonard T. Kurland), central nervous system infections with 66 (Charles A. Kane), language disorders with 62 (Joe R. Brown), neurochemistry with 50 (Donald B. Tower and Maynard M. Cohen), neuroophthalmology with 41 (N. S. Schlezinger), and neuropathology with 41 (Lucien Rubenstein pinch-hitting for Erland Nelson). In addition, 63 general practitioners registered in a course on general neurology for the general practitioner, designed and given by Benjamin Boshes.... A total of 12 courses are being planned for the 1961 AAN Meeting which will include new courses on the legal aspects of neurology, newer concepts of human cerebral organization, and the electron microscope.

Cerebrovascular Disease Subject of International Colloquium

After the Twelfth Annual Meeting of the American Academy of Neurology April 25 through 30 in Miami Beach, 500 neurologists and scientists from 7 different countries (Belgium, Canada, Denmark, England, France, Sweden, and the United States) met in a two-day colloquium* on the pathology, diagnosis, and treatment of cerebrovascular disease. The meeting was chaired by A. L. Sahs. Among the topics considered were predisposing neuropathology (A. B. Baker); mechanisms of brain vessel injury (W. E. Stehbens, Oxford); organization and distribution of major cerebral vessels (H. Kaplan, H. Vander Eecken, Ghent, and R. Berry, Philadelphia); alterations in blood flow (L. Sokoloff, N. Lassen, Copenhagen, and P. Scheinberg); brain mechanisms for controlling its own blood supply (J. S. Meyer, F. Gotch, and David Ingvar, Lund); and advances in angiography (J. W. D. Bull, London, J. M. Taveras, and O. Sugar). Also discussed was the use of "ophthalmodynamometry" by J. Toole (Philadelphia), L. Crevasse,

*Cosponsored by the American Academy of Neurology and the National Institute of Neurological Diseases and Blindness (Bethesda)

and A. Heyman (Durham). The value of the electroencephalogram for detecting variations in blood flow was described by H. Gastaut (Marseille), C. E. Wells, and S. Weiss (St. Louis). Finally, the results of controlled studies, both medical and surgical, were concerned, including the NINDB cooperative studies on anticoagulant therapy and the surgical treatment of intracranial aneurysms; studies on the surgical replacement of large arteries of the neck (M. DeBakey and S. Gurdjian, Detroit); and the independent studies of John Marshall (London) on anticoagulant therapy and of Lawrence Walsh (London) on treatment of aneurysms.... After the sessions, a small planning group under Chairman R. P. Schmidt met to map out promising new vistas of research in this field.

Pennsylvania Hospital Organizes New Neurology Department The Pennsylvania Hospital announces the creation of a newly formed teaching department of neurology under the direction of Frank A. Elliott, Professor of Clinical Neurology at the University of Pennsylvania. Dr. Elliott is a Queen Square man, having received his training under Francis M. R. Walsh, Gordon Holmes, Charles P. Symonds, and George Riddoch. The newly created department comprises a clinical service, a neurochemistry laboratory, a new electroencephalography department, and modern facilities for perimetry and neuroradiology. In the process of active development is a neuropathology laboratory under Sumner Zacks (formerly of the Armed Forces Institute of Pathology), which will provide for electromicroscopy, experimental neuropathology, and histochemistry. The current personnel consists of a first assistant, J. J. Pegues, 2 Ph.D's, and 3 graduate technicians in the neurochemistry laboratory and 1 resident in neurology. Increase in the number of neurologic residents is expected. The residency training program has received AMA approval. Inquiries should be addressed to Dr. Frank A. Elliott, Professor of Clinical Neurology, Pennsylvania Hospital, Eighth and Spruce Streets, Philadelphia 7.

Boshes Named National Secretary Benjamin Boshes (Northwestern Medical School, 303 E. Chicago Avenue, Chicago 11) has been appointed jointly by the American Academy of Neurology and the American Neurological Association to serve as National Secretary to the World Federation of Neurology, with headquarters in Antwerp. The appointment was made by the 2 societies upon the recommendation of the AAN-ANA joint committee* (See NEWSLETTER, February 1960) on international representation of American neurology. The WFN national secretary and the national delegate, H. Houston Merritt, should not be confused with the national delegate, James L. O'Leary and alternate, Bernard J. Alpers, to the Seventh International Neurological Congress to be

*Members of this Committee are Roland P. Mackay, Joint Chairman, J. L. O'Leary, Russell N. DeJong, and Joseph Foley for the AAN and B. J. Alpers, H. H. Merritt, and Fred Plum for the ANA.

held in Rome in 1961. The President of the Rome Congress is Professor Mario Gozzano and the Secretary-General is Giovanni Alemà, Viale Università, 30, Rome.

Neurosurgeons To Meet in Mexico City The Ninth Latin American Congress of Neurosurgery will be held in Mexico City under the Presidency of Dr. Manuel M. Velasco-Suárez. Meeting with the neurosurgeons will be the Fifth Latin American Congress of Electroencephalography and Clinical Neurophysiology (Dr. Carlos Villavicencio, President, and Dr. J. Hdez Peniche, Secretary) and an International Symposium of Neurologic Research (Dr. John D. French and Dr. H. W. Magoun, Presidents, and Dr. Raúl Hernández Peón, Coordinator). These meetings will be held October 4 through 10, 1961. Inquiries should be addressed to IX Congreso Latinamericano De Neurocirugia, Tonalá No. 15, Mexico 7, D.F.

Cushing Society Elects New Officers At its annual meeting in San Francisco April 14 through 16, the Harvey Cushing Society elected J. Grafton Love, President; Leonard T. Furlow, President-Elect; John Raaf, Vice-President; Hendrik J. Svien, Secretary; Eben Alexander, Jr., Treasurer; and Louise Eisenhardt, Historian.... The 1961 meeting of the Harvey Cushing Society will be held at the Hotel Del Prado in Mexico City April 17 through 19. Dr. Manuel Sanchez Garibay is chairman of local arrangements.

Key Staff Changes at NIH Surgeon General Leroy E. Burney of the Public Health Service announced 3 key staff changes which will become effective July 1. David E. Price, now chief of the bureau of state services will become deputy director of the National Institutes of Health, a position which has been vacant since the retirement of C. J. Van Slyke last December. Kenneth M. Endicott, now an associate director of the National Institues of Health, will be director of the National Cancer Institute, succeeding John R. Heller, who has been granted leave to accept the presidency of the Sloan-Kettering Memorial Cancer Center in New York City.

Briefs The French Society of Neurology (Société Française de Neurologie) staged its Twenty-fourth International Neurologic Reunion at the Salpetrière May 31 and June 1. The central topic of the scientific sessions was the apraxias under the direction of Professor H. Hécaen. The reunion was followed on June 2 by the regular monthly meeting of the French society.... Peter Kellaway is now President and William Caveness President-Elect of the American Epilepsy Society. H. Houston Merritt represents the Society as Vice-President for the International League against Epilepsy. Members of the Council are Richard B. Richter, Douglas

Davidson, Sidney Carter, and Robert Aird. Continuing as Secretary and Treasurer, respectively, are James W. Crawley and Madison H. Thomas. The next annual meeting of the society will be held December 8, 1960, in New York City.... The French Republic issued a new postage stamp on June 13 to honor the French neurologist, Jean-Martin Charcot (1825-1893).... Ellsworth C. Alvord, Jr., formerly of Baylor University, has accepted an appointment in neuropathology at the University of Washington in Seattle.... Glenn A. Drager, formerly a member of the staff of G. Milton Shy at the National Institute of Neurological Diseases and Blindness, has now joined the Department of Neurology at Baylor University College of Medicine.

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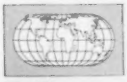

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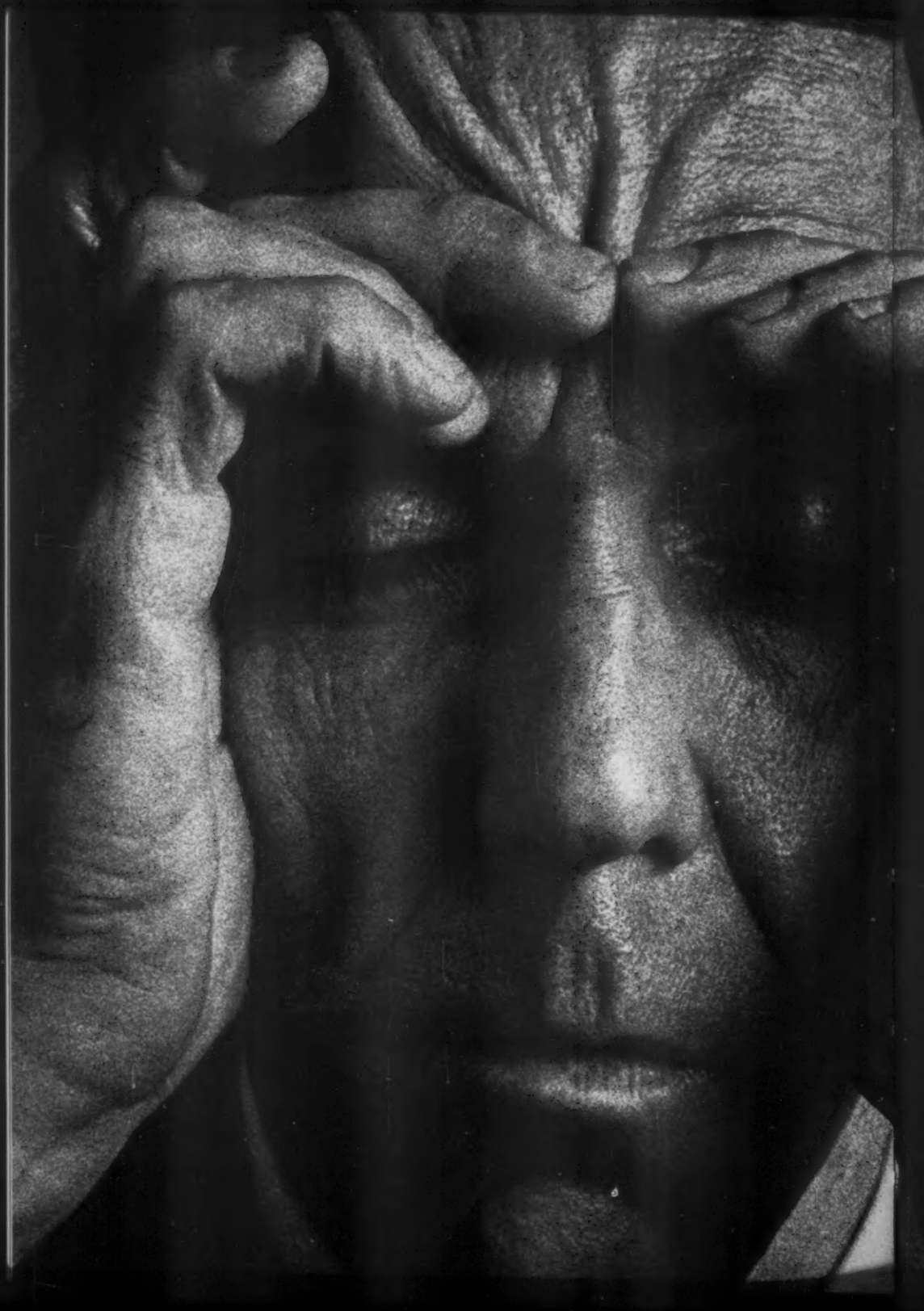

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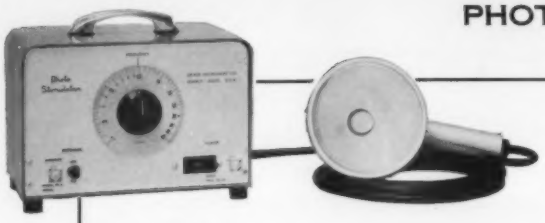

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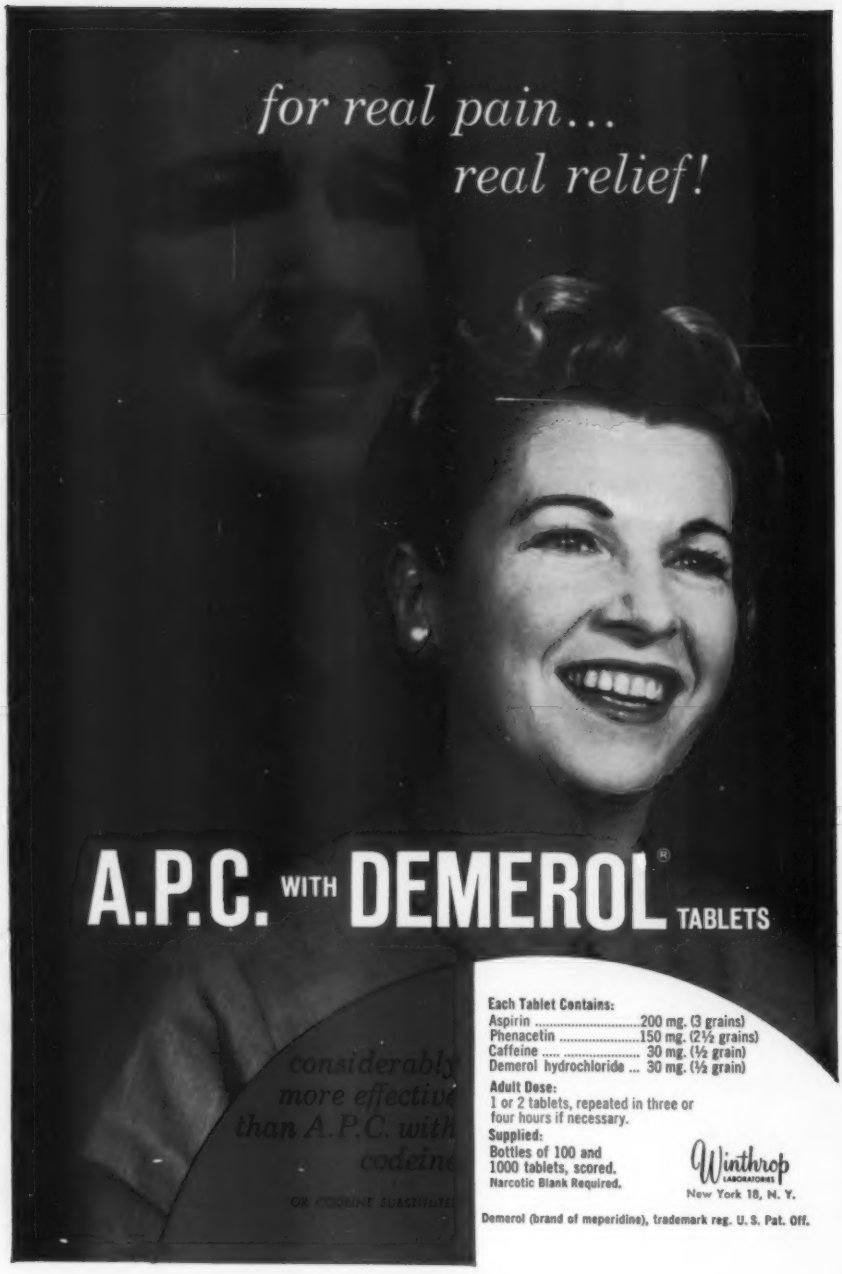
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